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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational

farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al., Science, 260*:1934-1937 (1993) and G.L. James *et al., Science, 260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al., Proc. Natl. Acad. Sci U.S.A., 91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al., Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al., ibid*; Casey *et al., ibid*; Schafer *et al., Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor

of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, *88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, *37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

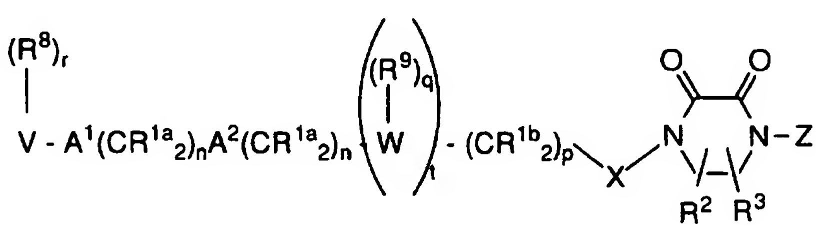
It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds

of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic 2,3-diketopiperazine-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formula A:



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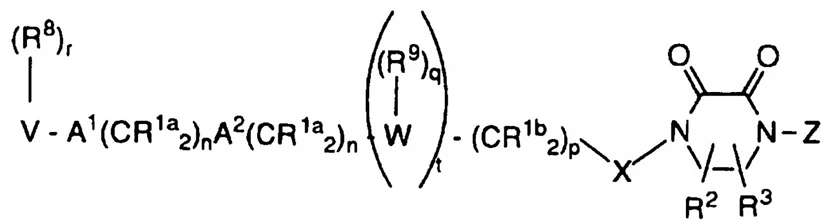
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



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wherein:

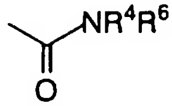
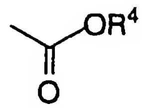
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

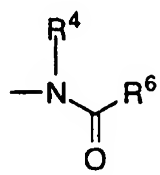
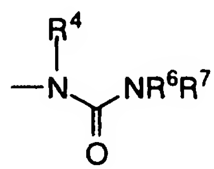
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

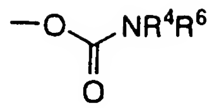
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

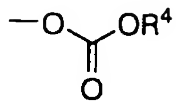
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

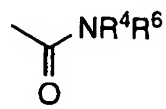
 and ,

wherein the substituted group is substituted with one or more of:

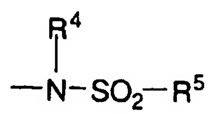
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^4$,
   c) $(CH_2)_pNR^4R^6$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl, or
   h) SR^5, $S(O)R^5$, SO_2R^5,
2) C_{3-6} cycloalkyl,
3) OR^4,
4) SR^5, $S(O)R^5$, or SO_2R^5,
5) $-NR^4R^6$,
6)  ,
7)  ,

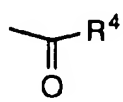
8)  ,

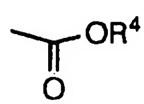
9)  ,

10)  ,

11) $-SO_2-NR^4R^6$,

12)  ,

13)  ,

14)  ,

15) N_3,

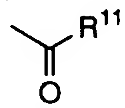
16) F, or

17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

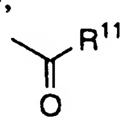
and R^2 and R^3 are optionally attached to the same carbon atom;

R^4, R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^4 and R^6 may be joined in a ring;
R^6 and R^7 may be joined in a ring;

R^5 is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, O, $-N(R^{10})$-, $-S(O)_2N(R^{10})$-, $-N(R^{10})S(O)_2$- and $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, $-CH_2-$, -C(=O)-, or $-S(=O)_m-$;

Z is selected from:

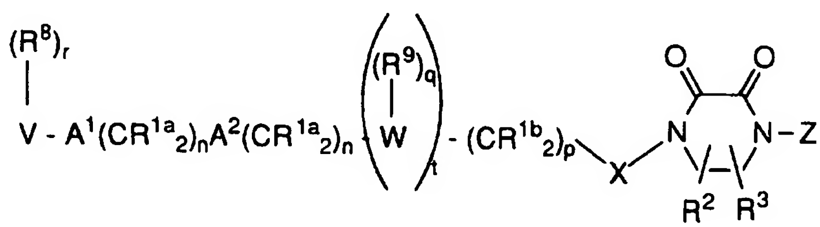
1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   b) aryl or heterocycle,
   c) halogen,
   d) OR^4,
   e) NR^4R^6,
   f) CN,
   g) NO_2,
   h) CF_3;
   i) $-S(O)_mR^5$,
   j) $-C(O)NR^4R^6$, or
   k) C_3-C_6 cycloalkyl; and
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
   a) C_{1-4} alkoxy,
   b) NR^4R^6,
   c) C_{3-6} cycloalkyl,

d) $-NR^4C(O)R^6$,
e) HO,
f) $-S(O)_mR^5$,
g) halogen, or
h) perfluoroalkyl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
q is	1 or 2;
r is	0 to 5, provided that r is 0 when V is hydrogen;
t is	0 or 1; and
u is	4 or 5;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula:



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wherein:

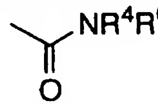
R^{1a} is independently selected from: hydrogen and C_1-C_6 alkyl;

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and $-N(R^{10})_2$;

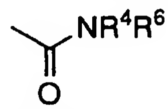
R^3 is selected from H and CH_3;

R^2 is selected from H;



;

or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^4,
4) SR^5, SO_2R^5, or
5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:
a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$- and $S(O)_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl and isoquinolinyl;

X is $-CH_2-$ or $-C(=O)-$;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   b) aryl or heterocycle,
   c) halogen,
   d) OR^4,
   e) NR^4R^6,
   f) CN,
   g) NO_2,
   h) CF_3;
   i) $-S(O)_mR^5$,
   j) $-C(O)NR^4R^6$, or
   k) C_3-C_6 cycloalkyl; and

2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted

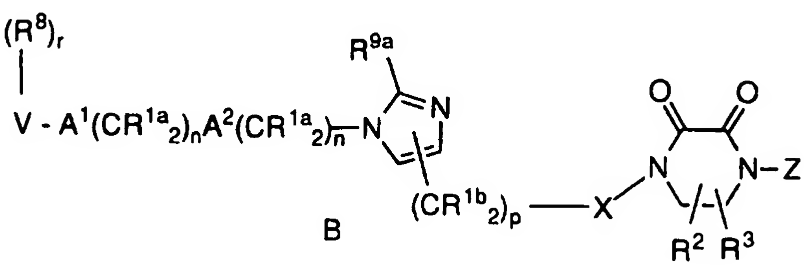
C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^4R^6,
c) C_{3-6} cycloalkyl,
d) $-NR^4C(O)R^6$,
e) HO,
f) $-S(O)_mR^5$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
t is 0 or 1; and
u is 4 or 5;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula B:



B

wherein:

R^{1a} is selected from: hydrogen and C_1-C_6 alkyl;

R^{1b} is independently selected from:

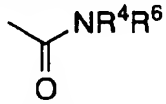
a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

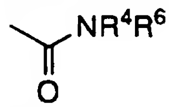
R^3 is selected from H and CH_3;

R^2 is selected from H;



;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^4,
4) SR^5, SO_2R^5, or
5) 

;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is -CH_2- or -C(=O)-;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
    a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
    b) aryl or heterocycle,
    c) halogen,
    d) OR^4,
    e) NR^4R^6,
    f) CN,
    g) NO_2,
    h) CF_3;
    i) $-S(O)_mR^5$,
    j) $-C(O)NR^4R^6$, or
    k) C_3-C_6 cycloalkyl; and

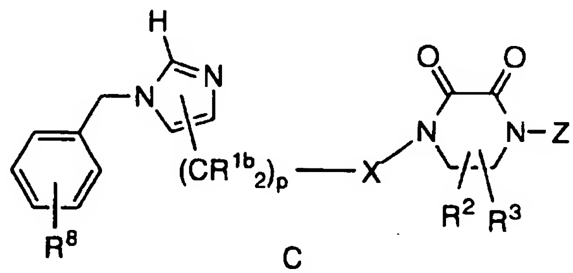
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
    a) C_{1-4} alkoxy,
    b) NR^4R^6,
    c) C_{3-6} cycloalkyl,
    d) $-NR^4C(O)R^6$,
    e) HO,
    f) $-S(O)_mR^5$,
    g) halogen, or
    h) perfluoroalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula C:

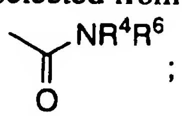


C

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

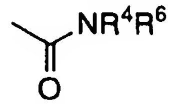
R^3 is selected from H and CH_3;
R^2 is selected from H;



;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:
1) aryl,
2) heterocycle,
3) OR^4,

4) SR^5, SO_2R^5, or

5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is $-CH_2-$ or $-C(=O)-$;

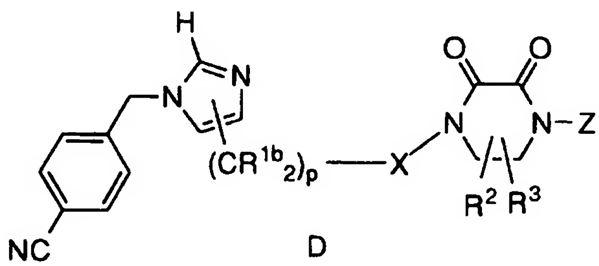
Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   b) aryl or heterocycle,
   c) halogen,
   d) OR^4,
   e) NR^4R^6,
   f) CN,
   g) NO_2,
   h) CF_3;
   i) $-S(O)_mR^5$,
   j) $-C(O)NR^4R^6$, or
   k) C_3-C_6 cycloalkyl; and
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
   a) C_{1-4} alkoxy,
   b) NR^4R^6,
   c) C_{3-6} cycloalkyl,
   d) $-NR^4C(O)R^6$,
   e) HO,
   f) $-S(O)_mR^5$,
   g) halogen, or
   h) perfluoroalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



D

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^2 and R^3 are independently selected from: hydrogen and C_1-C_6 alkyl;

R^4 and R^6 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is $-CH_2-$ or $-C(=O)-$;

Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic heteroarylmethiyl, mono- or bicyclic arylsulfonyl or mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^4R^6,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^5$, or
   g) $-C(O)NR^4R^6$,
2) aryl or heterocycle,
3) halogen,
4) OR^4,
5) NR^4R^6,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^5$,

10) -C(O)NR^{4}R^6, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds of this invention are as follows:

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,3-dione

(S)-5-*n*-butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-2,3-piperazinedione

1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,3-dione

4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazine-2,3-dione

(S) -5-Benzyl-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenyl-2,3-piperazinedione

(S)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione

4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-1-phenylpiperazine-2,3-dione

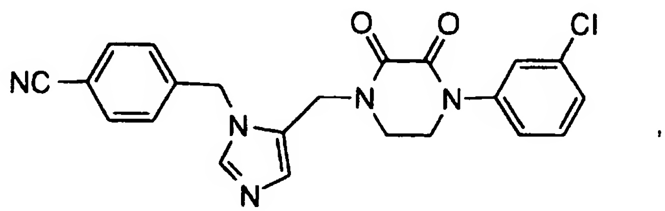
1-(4-imidazolyl)-4-(2,3-dimethylphenyl)piperazine-2,3-dione

1-[1-(4-cyanobenzyl)-5-imidazolyl]-4-(2,3-dimethylphenyl)piperazine-2,3-dione

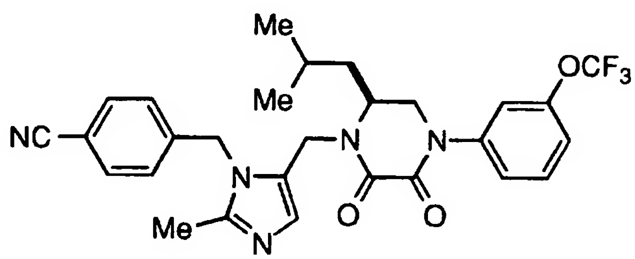
or a pharmaceutically acceptable salt or optical isomer thereof.

Specific examples of the compounds of the invention are:

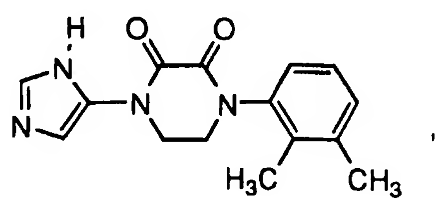
4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,3-dione



(S)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione



1-(4-imidazolyl)-4-(2,3-dimethylphenyl)piperazine-2,3-dione



or a pharmaceutically acceptable salt or optical isomer thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable

(e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl,

pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the definition of R^2 and R^3, the term "the substituted group" intended to mean the substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substitutent(s) R^2 and R^3 are selected.

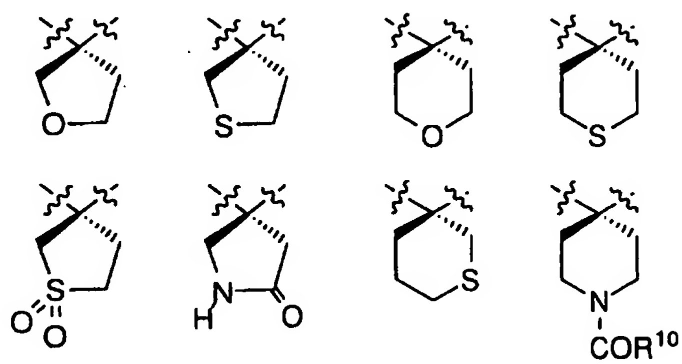
As used herein in the definition of R^4, R^5, R^6 and R^7, the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substitutents in addition to the point of attachment to the rest of the compound. Preferably, such substitutents are selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6\ alkyl)_2$, NO_2, CN, $(C_1\text{-}C_6$ alkyl)O-, -OH, $(C_1\text{-}C_6$ alkyl)$S(O)_m$-, $(C_1\text{-}C_6$ alkyl)C(O)NH-, H_2N-C(NH)-, $(C_1\text{-}C_6$ alkyl)C(O)-, $(C_1\text{-}C_6$ alkyl)OC(O)-, N_3,$(C_1\text{-}C_6$ alkyl)OC(O)NH-,

phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C_1-C_{20} alkyl.

As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

When R^2 and R^3 are combined to form - $(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

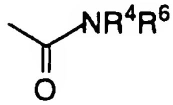
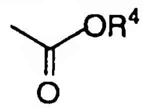


Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}$- or unsubstituted or substituted

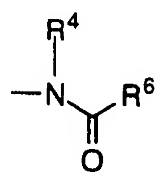
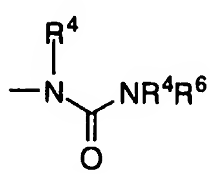
C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, -$N(R^{10})_2$, $R^{10}O$- and $R^{10}C(O)NR^{10}$-.

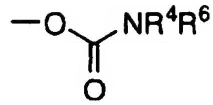
Preferably, R^2 is selected from: H,

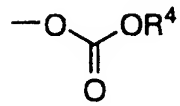
 ,  ,

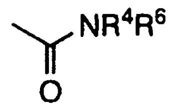
and an unsubstituted or substituted group, the group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl;

wherein the substituted group is substituted with one or more of:

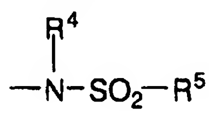
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^4$,
   c) $(CH_2)_pNR^4R^6$,
   d) halogen,
   e) CN,
2) C_{3-6} cycloalkyl,
3) OR^4,
4) SR^5, $S(O)R^5$, SO_2R^5,
5) $-NR^4R^6$,
6)  ,
7)  ,

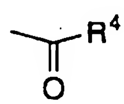
8)  ,

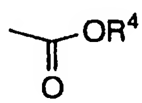
9)  ,

10)  ,

11) $-SO_2-NR^4R^6$,

12)  ,

13)  ,

14)  ,

15) N_3, or

16) F.

Preferably, R^3 is selected from: hydrogen and C_1-C_6 alkyl.

Preferably, R^4, R^6 and R^7 are selected from: hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^5 is unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^9 is hydrogen or methyl. Most preferably, R^9 is hydrogen.

Preferably, R^{10} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})- and-N(R^{10})S(O)$_2$-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, Z is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or substituted pyridyl, unsubstituted or substituted furanyl and unsubstituted or substituted thienyl. More preferably, Z is unsubstituted or substituted phenyl.

Preferably, X is -CH$_2$- or -C(=O)-.

Preferably, W is selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyyrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

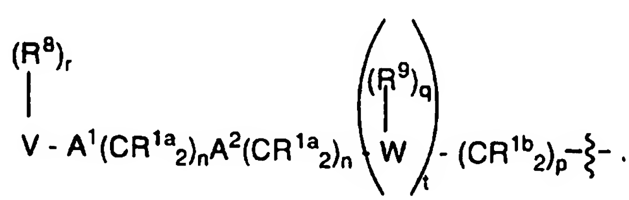
Preferably, n and r are independently 0, 1, or 2.

Preferably p is 0 or 1.

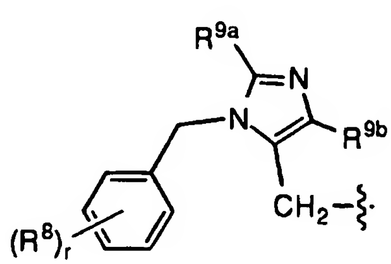
Preferably s is 0.

Preferably t is 1.

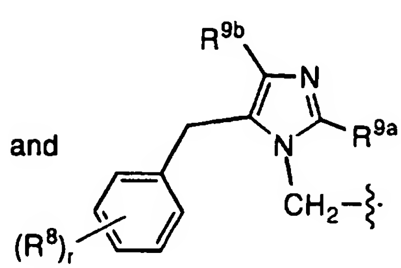
Preferably, the moiety



is selected from:



and



It is intended that the definition of any substituent or variable (e.g., R^{1a}, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-14, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

These reactions may be employed in a linear sequence

to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-14:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. 2,3-Diketopiperazines can be generally prepared as shown in Scheme 1. Amination of the suitably substituted 2-oxazolidinone I provides the diamine II. This is then reacted with methylchlorooxalate to provide the secondary amide III; acid deprotection provides the key intermediate IV. Ring closure to the diketopiperazine VI occurs concurrently with reductive alkylation with an aldehyde such as the protected imidazolyl aldehyde V. The imidazolyl protecting group may be removed under acidic conditions such as trifluoroacetic acid in methylene chloride. Alternatively, the imidazolyl may be alkylated and then deprotected to provide compounds such as VIII

The intermediate IV can be cyclized and reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75), from the appropriate amino acid (Scheme 2). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

As shown in Scheme 3, the imidazole acetic acid XVI can be converted to the acetate XVII by standard procedures, and the protected imidazole XVIII can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XIX. The ester is hydrolyzed and the acid converted to the acid chloride. Reaction with the suitably substituted lithium diketopiperazine XXI in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXII.

If the intermediate IV is cyclized/reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXIII in Scheme 4, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 4, 5). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXVII. In addition, the fully deprotected amino alcohol XXV can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXIX (Scheme 5), or tertiary amines.

The Boc protected amino alcohol XXV can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXX (Scheme 6). Treating XXV with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXX. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield, after deprotection, the ring-opened product XXXII.

In addition, the intermediate IV can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXV as shown in Scheme 7. When R' is an aryl group, XXXV can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXVI. Alternatively, the amine protecting group in XXXV can be removed, and O-alkylated phenolic amines such as XXXVII produced.

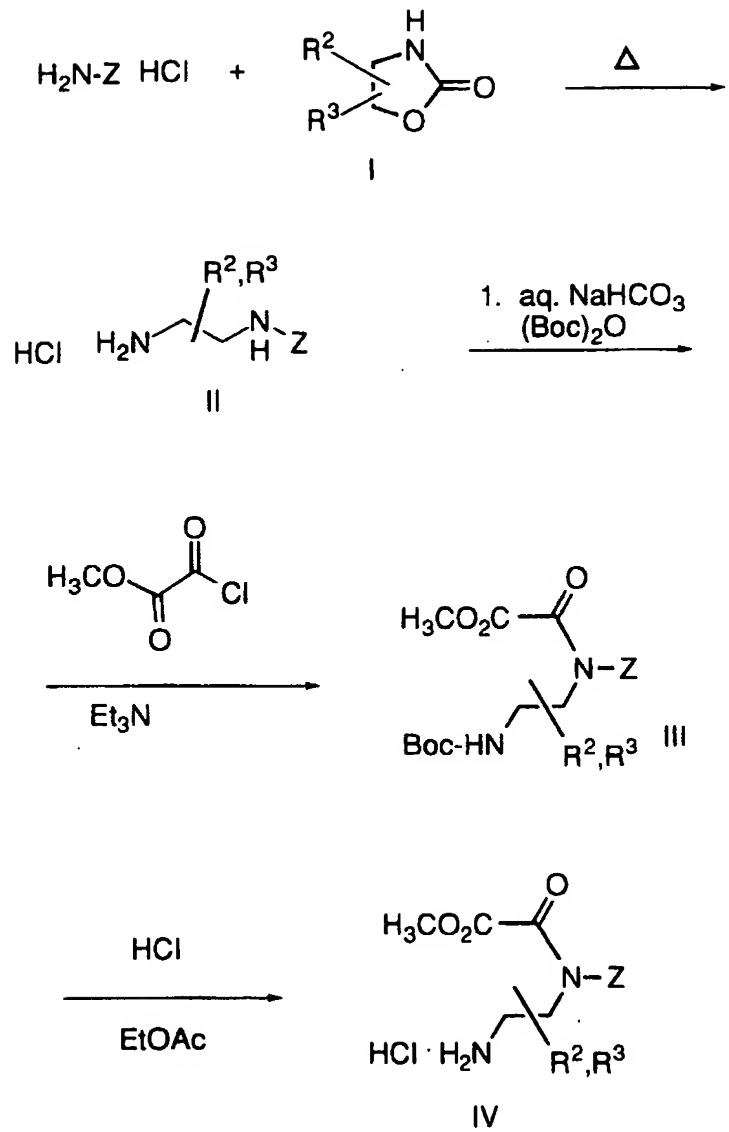
Reaction Scheme 8 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^4 and R^5 are combined to form - $(CH_2)_u$ -. For example, 1-amino-cyclohexan-1-al XXXVIII can be converted to the intermediate IXL essentially according to the procedures outlined in Schemes 1 and 2. The intermediate IXL can be deprotected as before, and carried on to final products as described in Schemes 3-7. It is understood that reagents utilized to provide the imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

Scheme 9 illustrates the use of an optionally substituted homoserine lactone XLII to prepare a Boc-protected intermediate XLIII. Intermediate XLIII may be deprotected and cyclized/reductively alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of diketopiperazine XLIV may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an the sulfide XLV. Diketopiperazine XLIV may also be oxidized to provide the carboxylic acid on diketo-piperazine XLVI, which can be further utilized to form an ester or amide moiety.

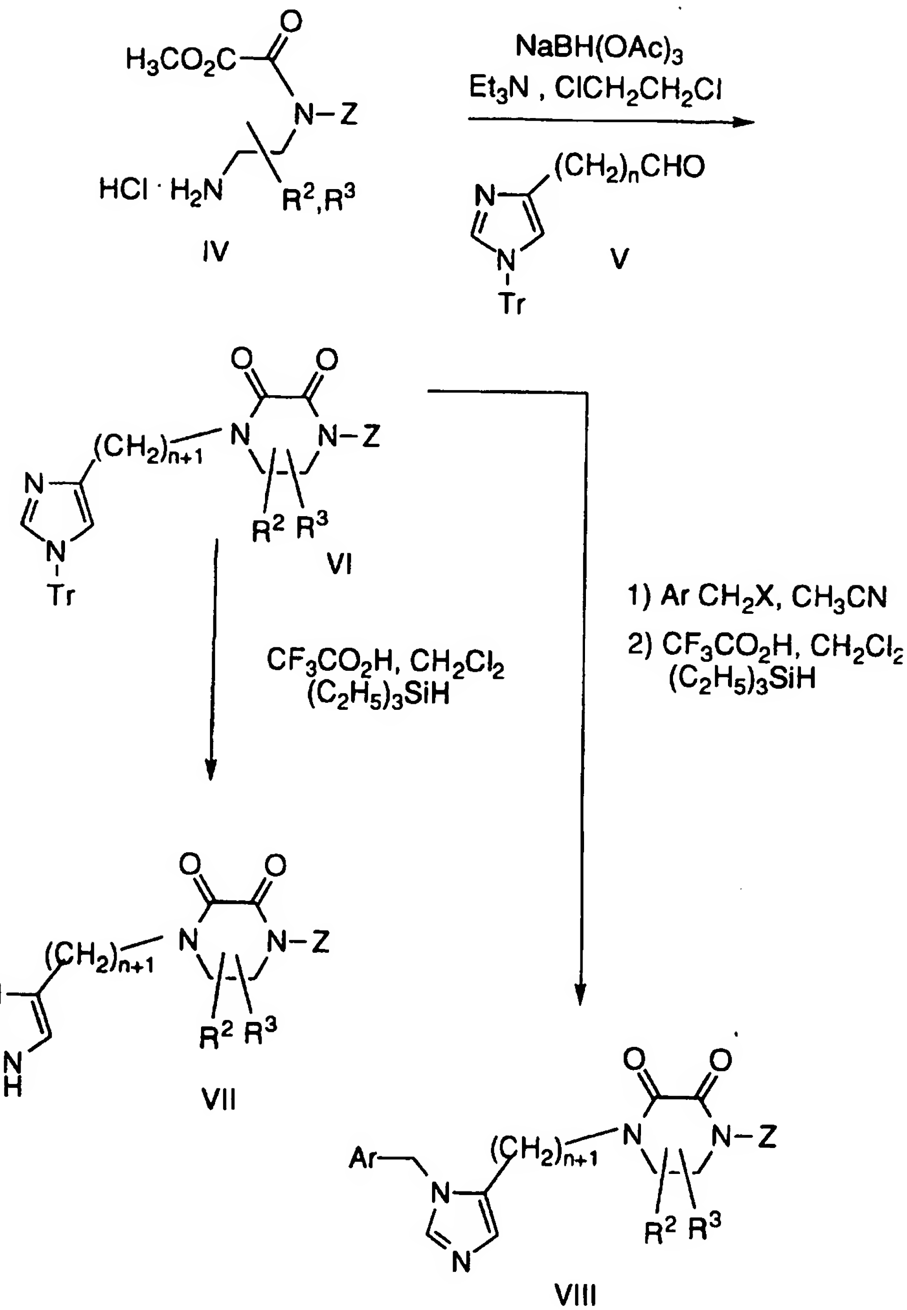
Aldehydes of the general formula IL which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 10 starting with the readily prepared imine XLVII.

Schemes 11-14 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

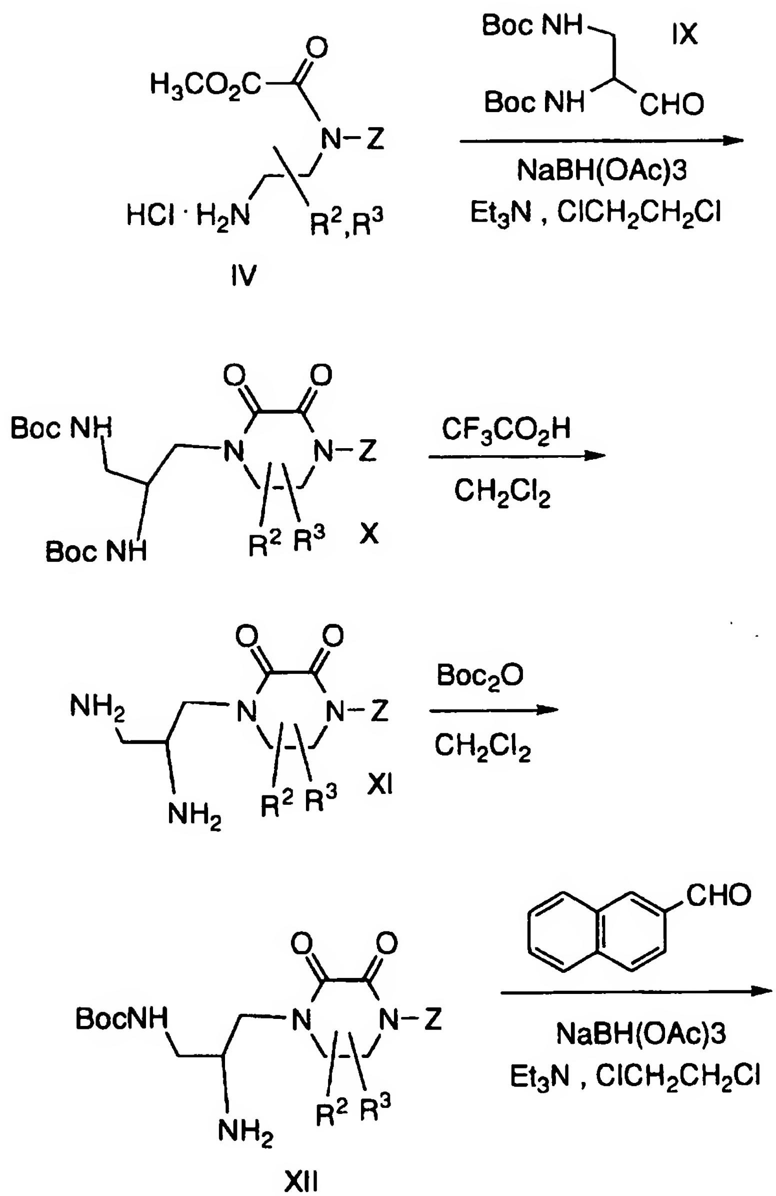
SCHEME 1


H₂N-Z HCl
Δ
I
HCl
II
1. aq. NaHCO₃
(Boc)₂O
Et₃N
Boc-HN
III
HCl
EtOAc
IV

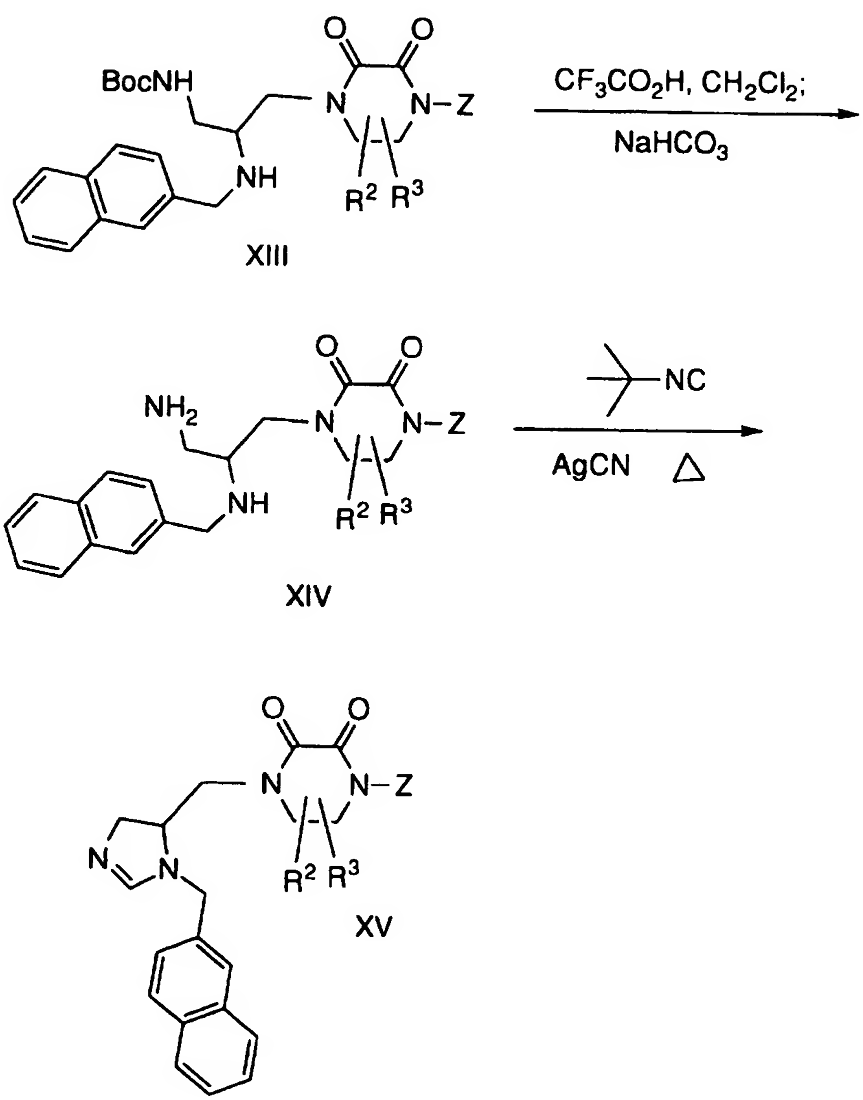
SCHEME 1 (continued)



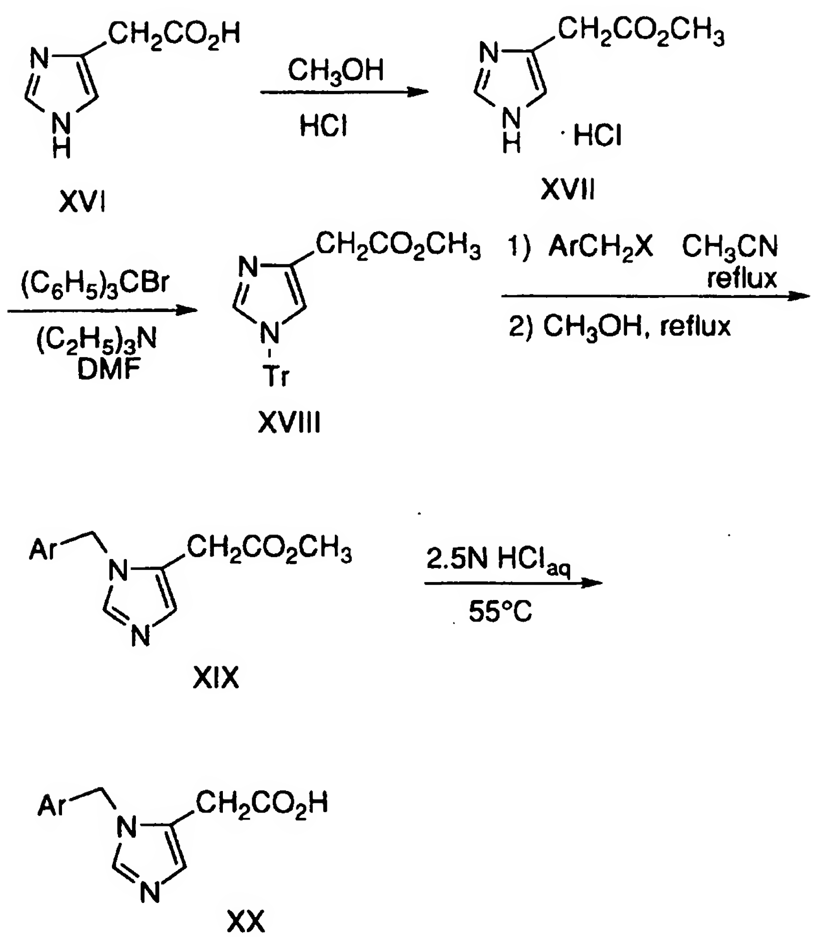
SCHEME 2


H3CO2C
O
N-Z
HCl · H2N
R2,R3
IV
Boc NH
IX
Boc NH
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl
Boc NH
O
O
N
N-Z
Boc NH
R2 R3
X
CF3CO2H
CH2Cl2
NH2
NH2
XI
Boc2O
BocNH
XII
CHO

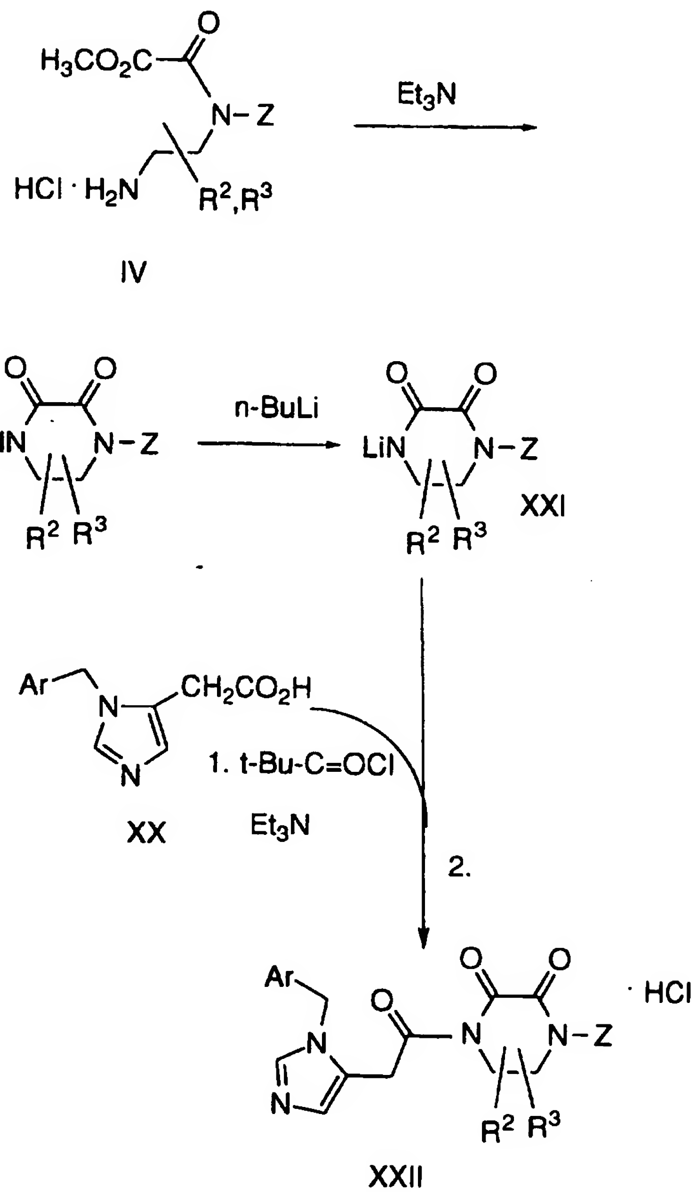
SCHEME 2 (continued)



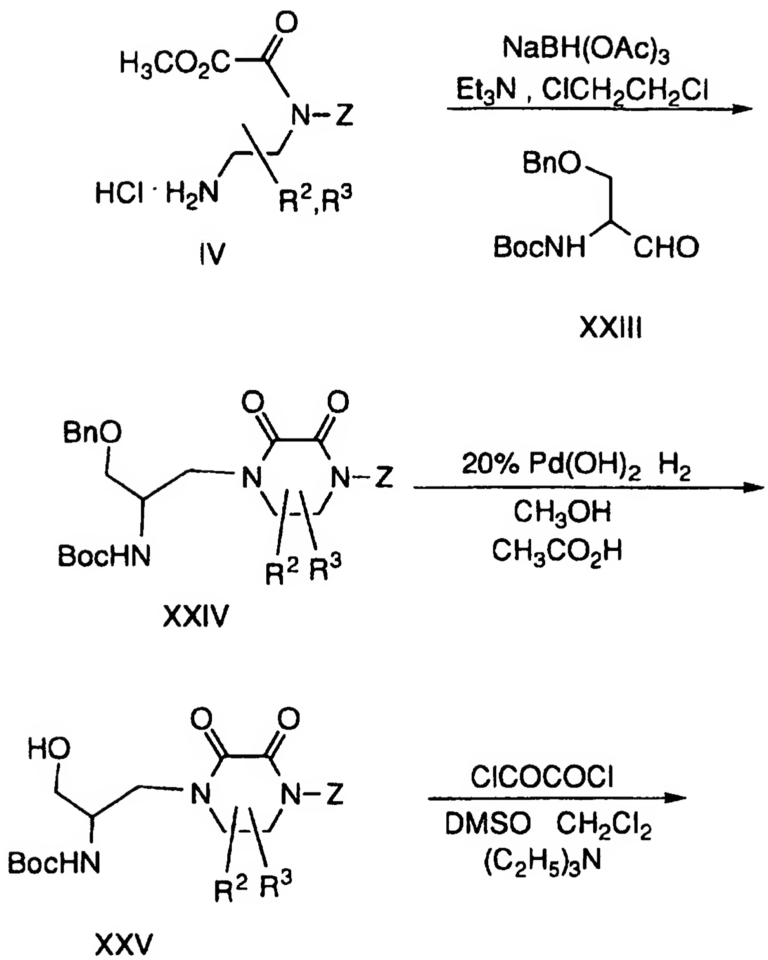
SCHEME 3


CH2CO2H
N
N
H
XVI
CH3OH
HCl
CH2CO2CH3
· HCl
XVII
(C6H5)3CBr
(C2H5)3N
DMF
Tr
XVIII
1) ArCH2X CH3CN
reflux
2) CH3OH, reflux
Ar
XIX
2.5N HClaq
55°C
XX

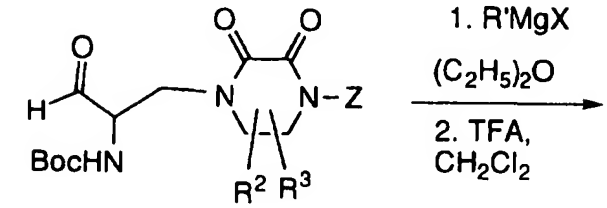
SCHEME 3 (continued)



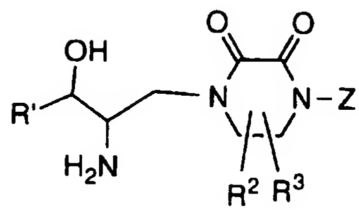
SCHEME 4


NaBH(OAc)3
Et3N , ClCH2CH2Cl
IV
XXIII
20% Pd(OH)2 H2
CH3OH
CH3CO2H
XXIV
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
XXV

SCHEME 4 (CONTINUED)

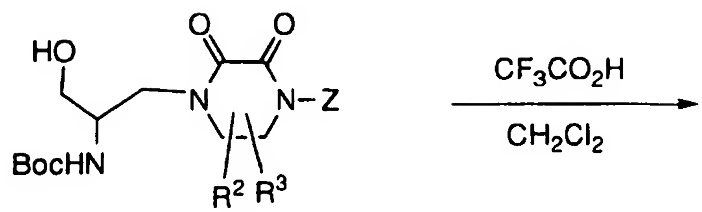


XXVI

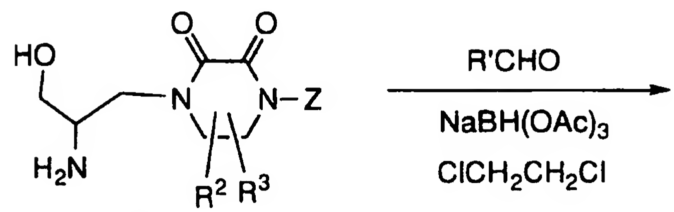


XXVII

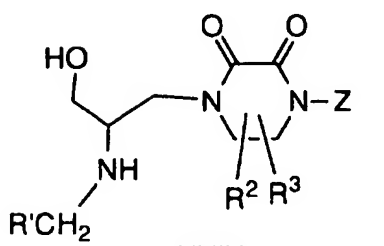
SCHEME 5



XXV

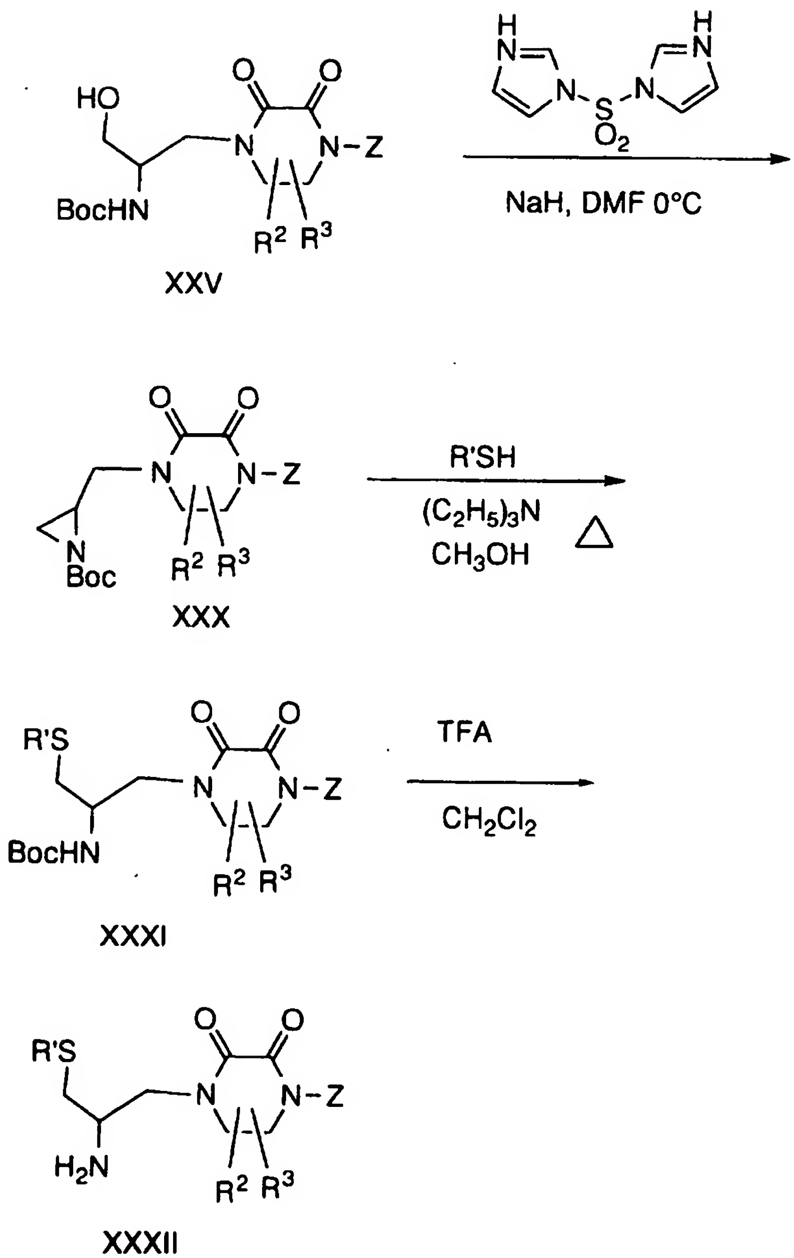


XXVIII

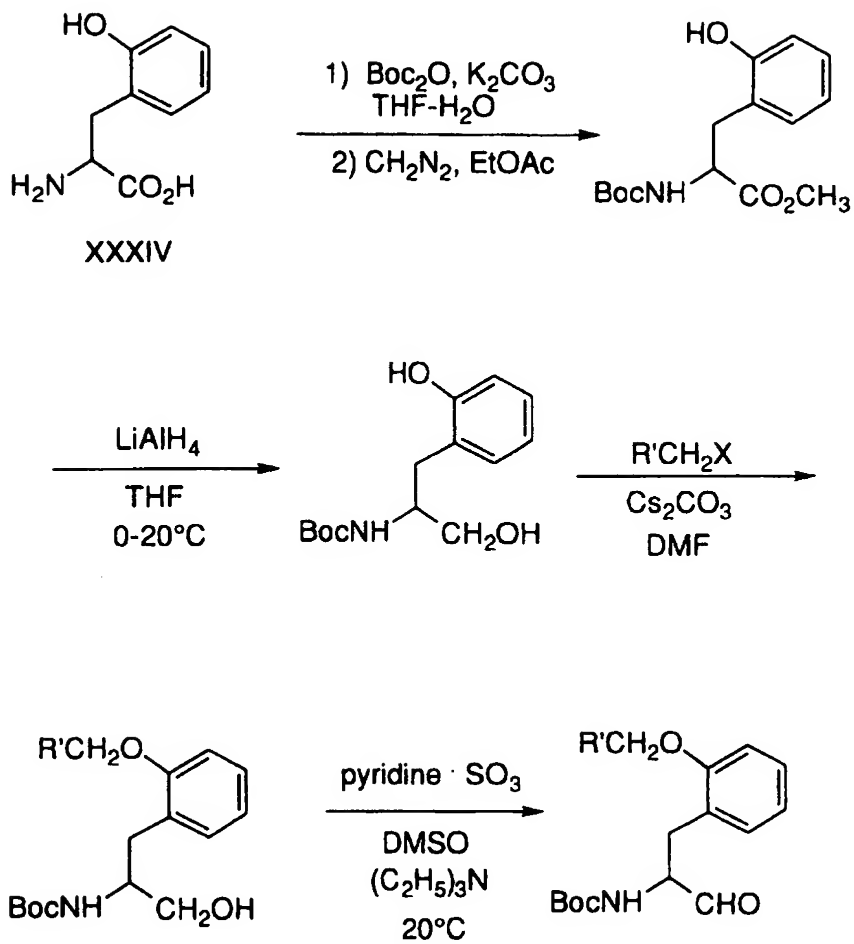


XXIX

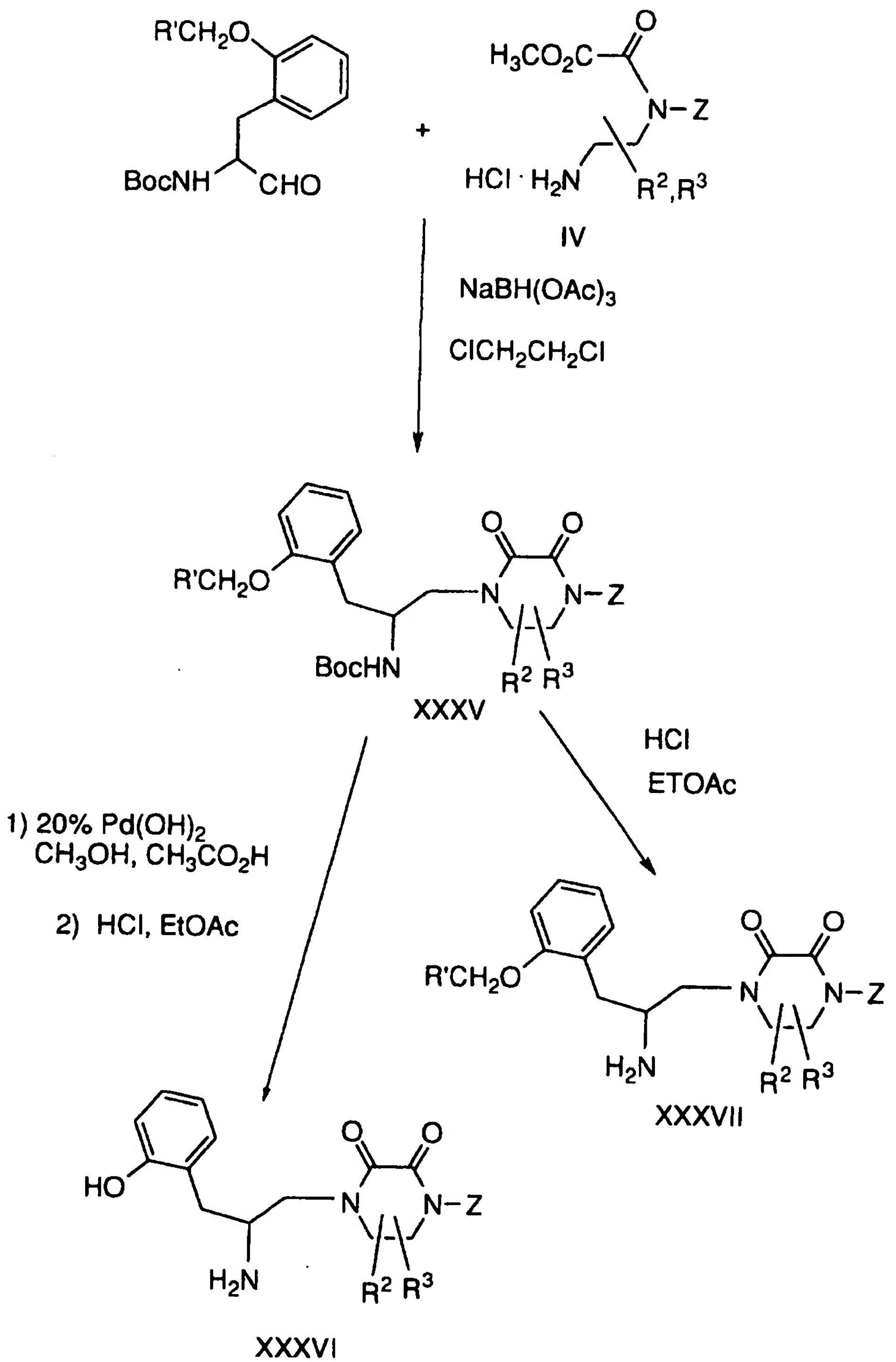
SCHEME 6


HO
BocHN
N
N-Z
R^2 R^3
XXV
NaH, DMF 0°C
XXX
R'SH
$(C_2H_5)_3N$
CH_3OH
Boc
R'S
XXXI
TFA
CH_2Cl_2
H_2N
XXXII

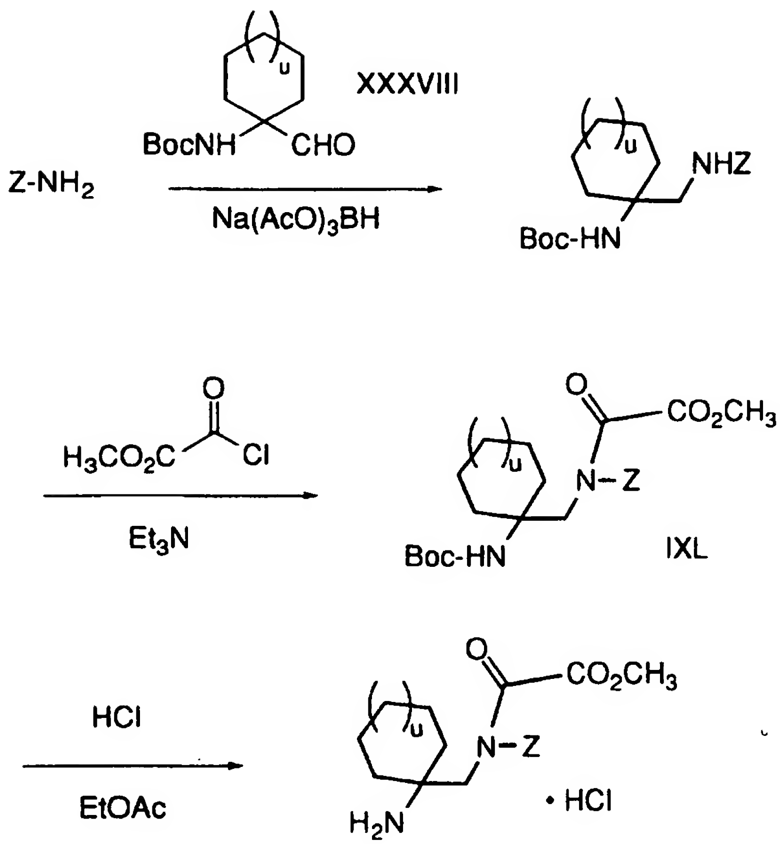
SCHEME 7


HO
H_2N
CO_2H
XXXIV
1) Boc_2O, K_2CO_3
THF-H_2O
2) CH_2N_2, EtOAc
HO
BocNH
CO_2CH_3
$LiAlH_4$
THF
0-20°C
HO
BocNH
CH_2OH
$R'CH_2X$
Cs_2CO_3
DMF
$R'CH_2O$
BocNH
CH_2OH
pyridine · SO_3
DMSO
$(C_2H_5)_3N$
20°C
$R'CH_2O$
BocNH
CHO

SCHEME 7 (continued)

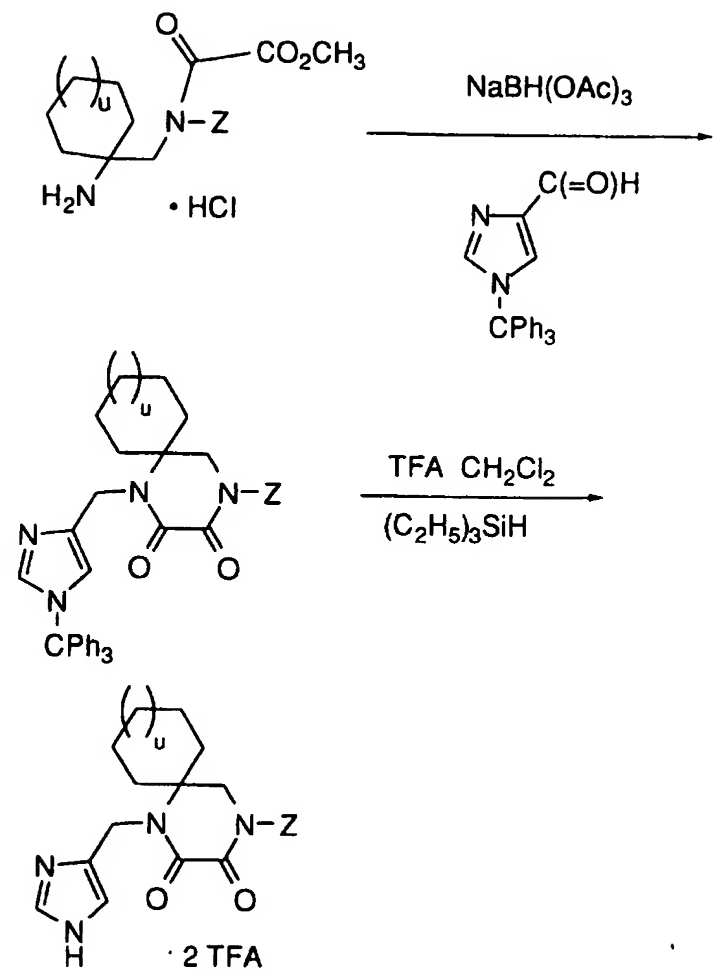


SCHEME 8


XXXVIII
BocNH
CHO
Z-NH2
Na(AcO)3BH
NHZ
Boc-HN
H3CO2C
Cl
O
Et3N
CO2CH3
N-Z
Boc-HN
IXL
HCl
EtOAc
H2N
• HCl
u

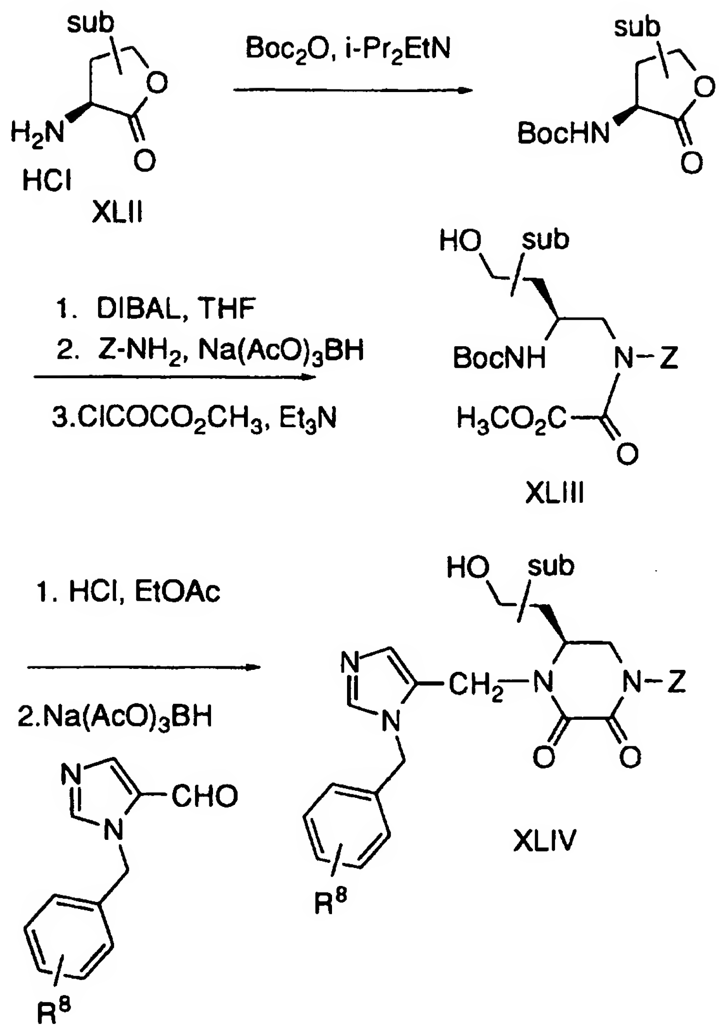
XL

SCHEME 8 (continued)



XLI

SCHEME 9

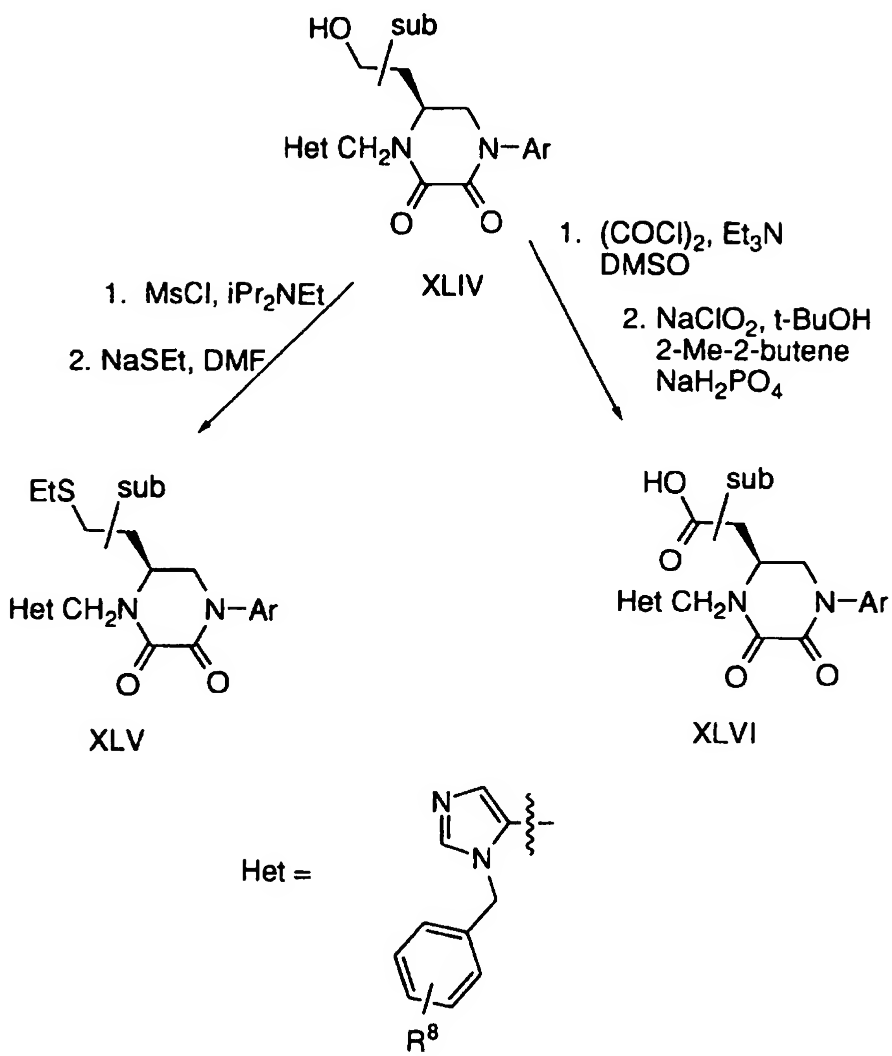


XLII

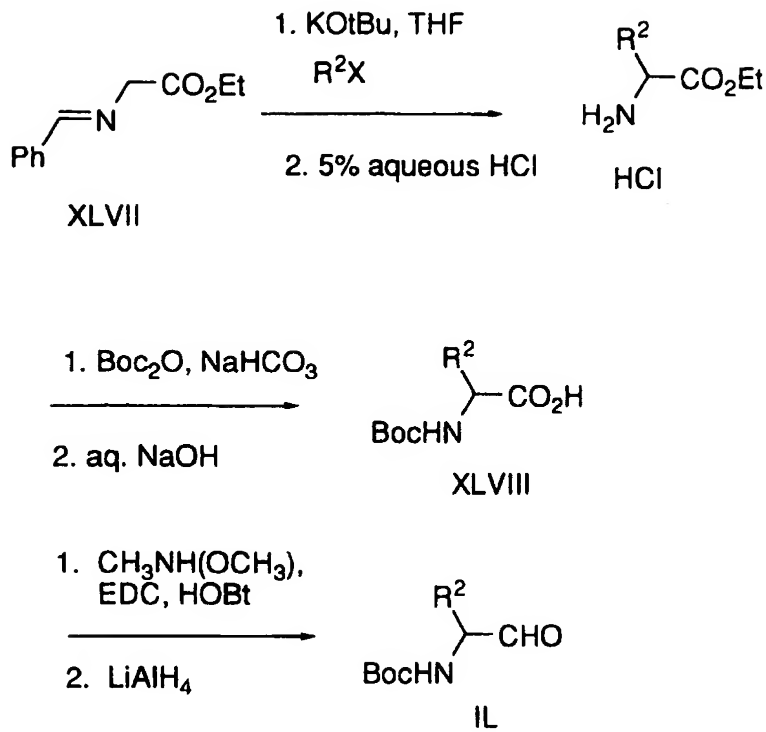
XLIII

XLIV

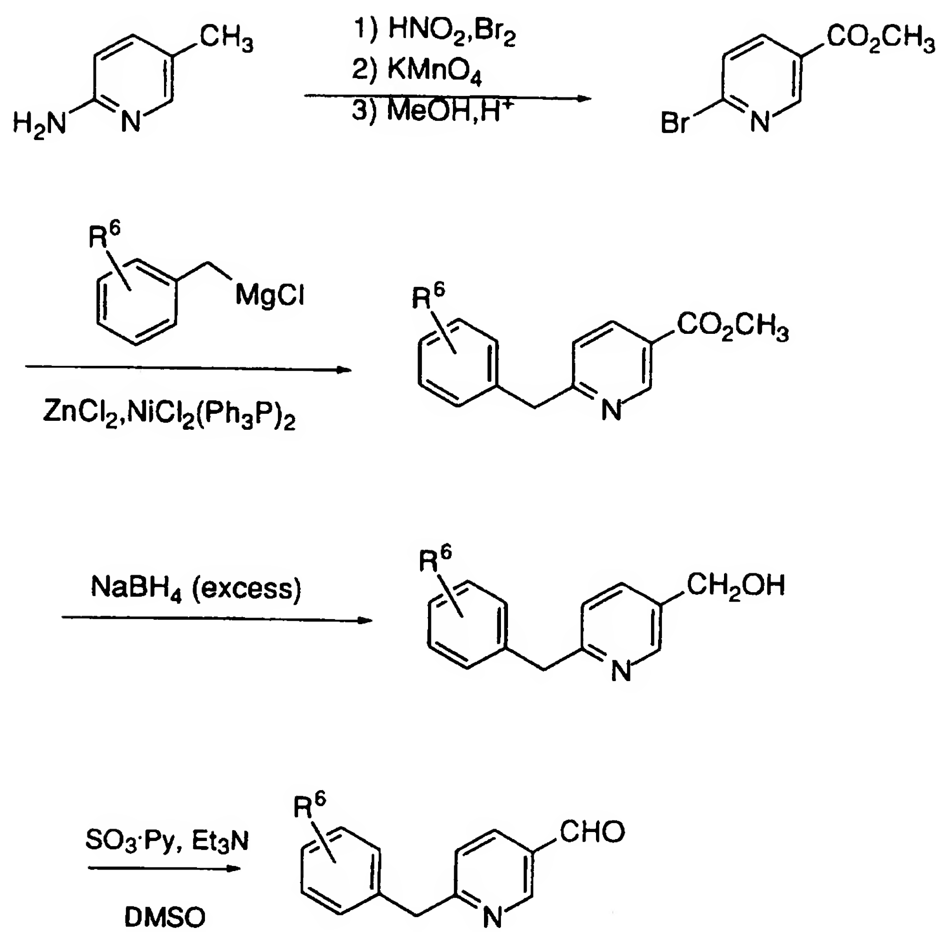
SCHEME 9 (continued)



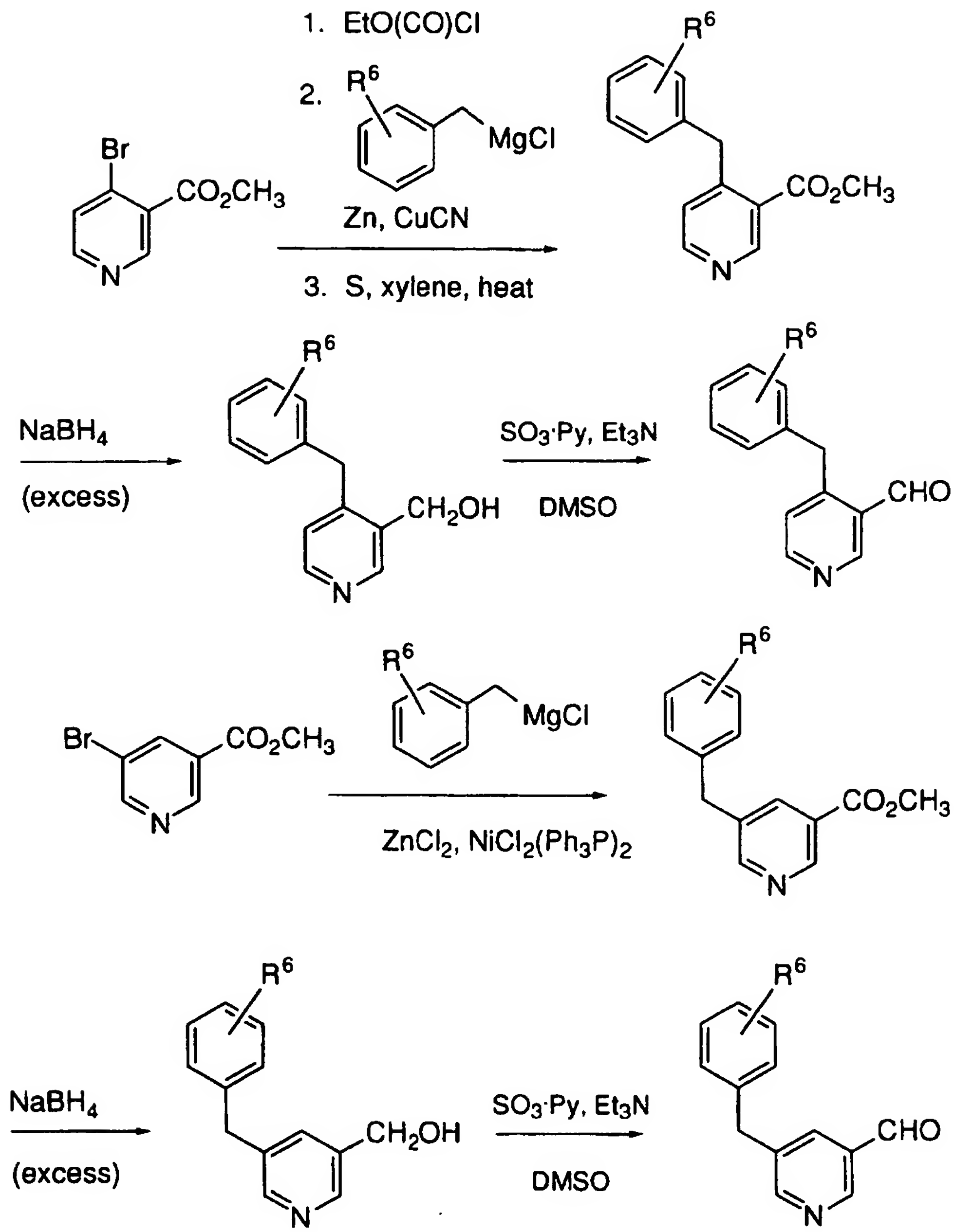
SCHEME 10


CO2Et
N
Ph
XLVII
1. KOtBu, THF
R2X
2. 5% aqueous HCl
R2
CO2Et
H2N
HCl
1. Boc2O, NaHCO3
2. aq. NaOH
R2
CO2H
BocHN
XLVIII
1. CH3NH(OCH3),
EDC, HOBt
2. LiAlH4
R2
CHO
BocHN
IL

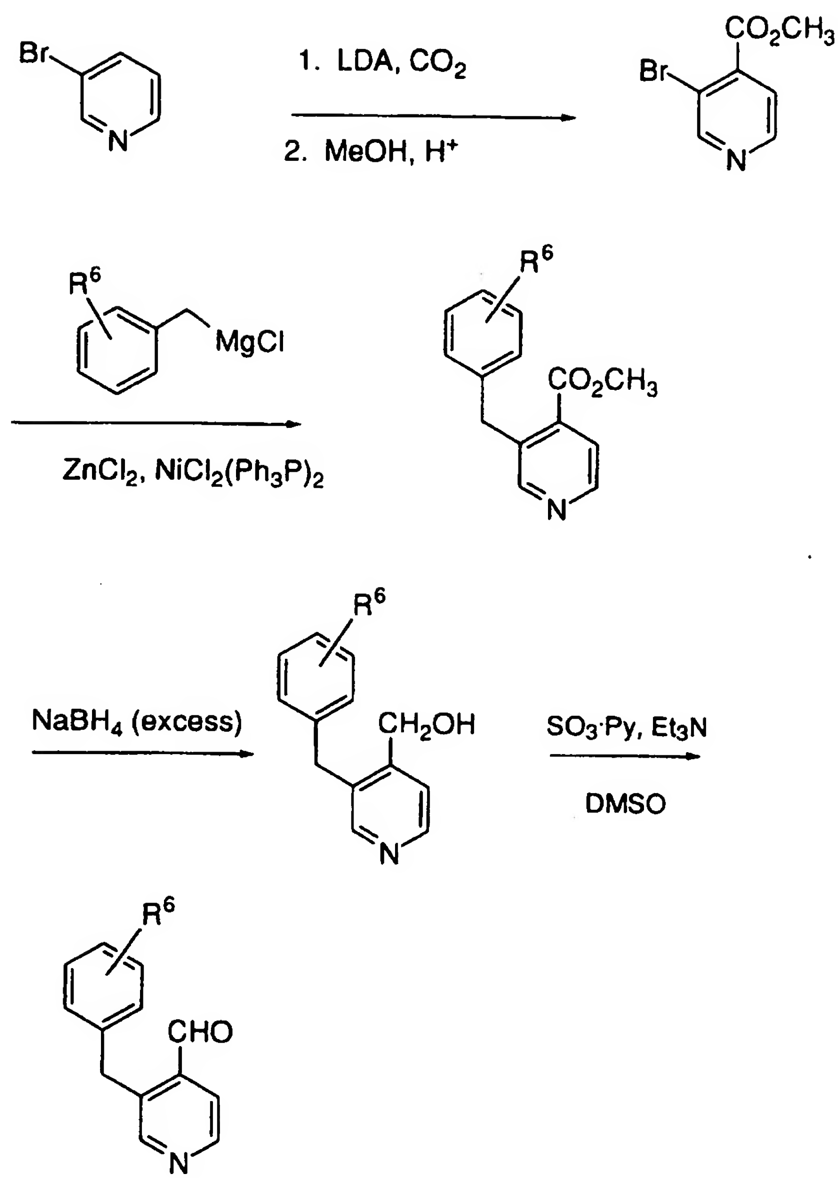
SCHEME 11


CH3
H2N
N
1) HNO2,Br2
2) KMnO4
3) MeOH,H+
CO2CH3
Br
N
R6
MgCl
ZnCl2,NiCl2(Ph3P)2
R6
CO2CH3
N
NaBH4 (excess)
R6
CH2OH
N
SO3·Py, Et3N
DMSO
R6
CHO
N

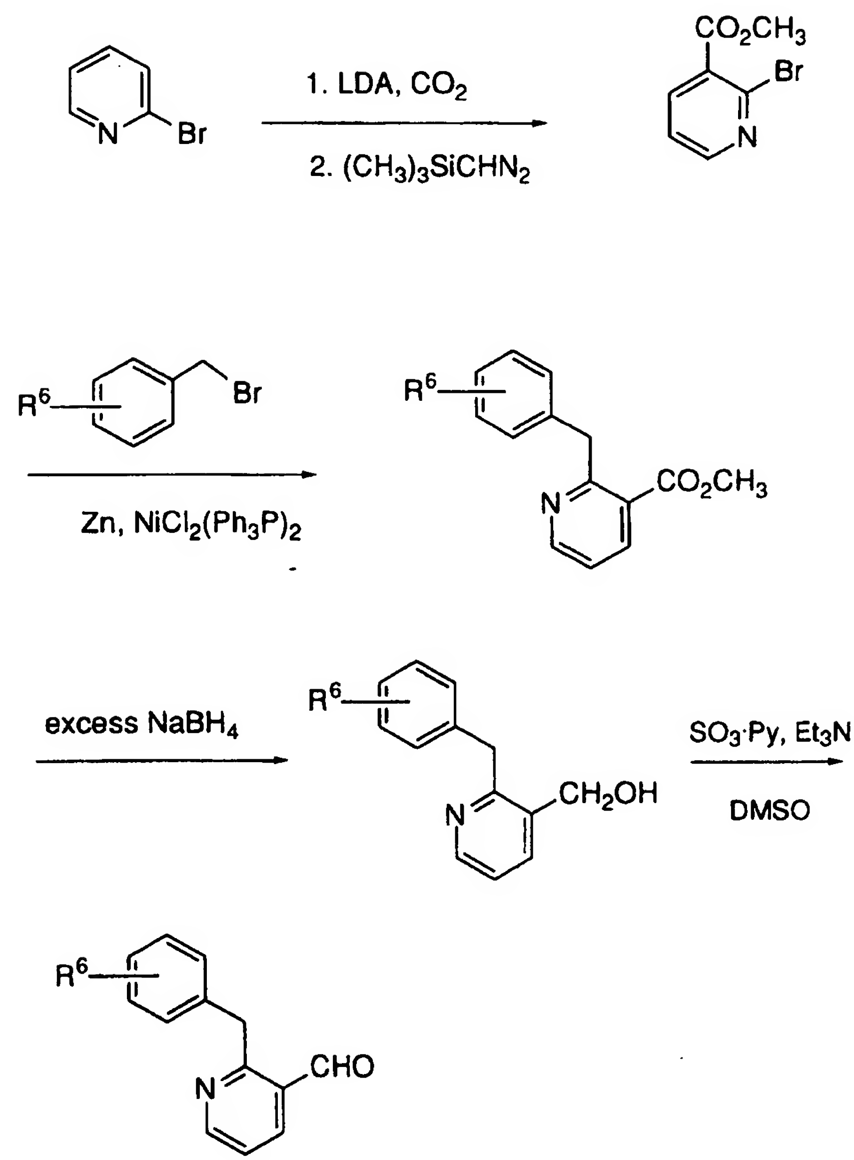
SCHEME 12


1. EtO(CO)Cl
2.
R^6
MgCl
Zn, CuCN
3. S, xylene, heat
Br
CO_2CH_3
N
NaBH$_4$
(excess)
CH_2OH
SO_3·Py, Et_3N
DMSO
CHO
ZnCl$_2$, NiCl$_2$(Ph$_3$P)$_2$

SCHEME 13


Br
1. LDA, CO_2
2. MeOH, H^+
CO_2CH_3
N
R^6
MgCl
$ZnCl_2$, $NiCl_2(Ph_3P)_2$
$NaBH_4$ (excess)
CH_2OH
$SO_3 \cdot Py$, Et_3N
DMSO
CHO

SCHEME 14



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine

pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two

portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,3-dione hydrochloride

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concen-

trated *in vacuo* to provide the crude product. The acetate was isolated as a white powder (85.8 g, 86% yield for two steps) which was sufficiently pure for use in the next reaction.

Step C: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60°C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid (50.4 g, 67% yield, 89% purity by HPLC) which was used in the next step without further purification.

Step D: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product (26.2 g, 82% yield) as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step E: Preparation of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde (18.7 g, 88% yield) as a white powder which was sufficiently pure for use in the next step without further purification.

Step F: Preparation of N-(3-chlorophenyl)ethylenediamine hydrochloride

To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0 °C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160 °C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

Step G: Preparation of *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl)ethylenediamine

The amine hydrochloride from Step F (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. $NaHCO_3$ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled carbamate (77 g, 100% yield for two steps, *ca.* 80% pure by ^1H NMR) as a brown oil which was used in the next step without further purification.

Step H: Preparation of methyl *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)oxalamide

A solution of the product from Step G (1.15 g, 4.26 mmol) and triethylamine (1.19 mL, 8.52 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C. Methyl chlorooxalate (0.431 mL, 4.68 mmol) was added dropwise, and the reaction was maintained at 0 °C with stirring. After 1 h, another portion of methyl chlorooxalate (0.20 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc and washed with water, sat. aq. NH_4Cl soln, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled compound which was used in the next step without further purification.

Step I: Preparation of methyl *N*-(2-aminoethyl)-*N*-(3-chlorophenyl)oxalamide hydrochloride

Through a solution of Boc-protected amine from Step H (1.0 g, 2.81 mmol) in 40 mL of EtOAc at 0°C was bubbled anhydrous HCl gas. After 40 minutes, nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a sticky white solid which was used in the next step without further purification.

Step J: Preparation of 4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)piperazine-2,3-dione hydrochloride

To a solution of the amine hydrochloride from Step I (400 mg, 1.37 mmol) in 5 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (1 g), followed by sodium triacetoxyborohydride (435 mg, 2.05 mmol). The aldehyde from Step E (375 mg, 1.78 mmol) was added, and the reaction was stirred overnight, allowing it to warm to room temperature. After 20 hours, the reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product

was taken up in 10 mL of CH_2Cl_2, and propylamine (2 mL) was added. The reaction was stirred for 12 hours, then concentrated *in vacuo*, and purified by silica gel chromatography (5-10% $MeOH/CH_2Cl_2$), then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo*. The titled product hydrochloride (190 mg) was isolated as a white solid.

FAB mass spectrum m/e 420 (M+1).

Analysis calculated for $C_{22}H_{18}ClN_5O_2$ • 1.40 HCl • 1.00 H_2O:

C, 54.05; H, 4.41; N, 14.32;

Found: C, 54.17; H, 4.42; N, 14.12.

EXAMPLE 2

(S)-5-*n*-butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-2,3-piperazinedione hydrochloride

Step A: Preparation of *N*-Methoxy-*N*-methyl 2(S)-(*tert*-butoxycarbonylamino)-hexanamide

2(S)-Butoxycarbonylaminohexanoic acid (24.6 g, 0.106 mol), *N,O*-dimethylhydroxylamine hydrochloride (15.5 g, 0.15 mol), EDC hydrochloride (22.3 g, 0.117 mol) and HOBT (14.3 g, 0.106 mol) were stirred in dry, degassed DMF (300 mL) at 20°C under nitrogen. *N*-Methylmorpholine was added to obtain pH 7. The reaction was stirred overnight, the DMF distilled under high vacuum, and the residue partitioned between ethyl acetate and 2% potassium hydrogen sulfate. The organic phase was washed with saturated sodium bicarbonate, water, and saturated brine, and dried with magnesium sulfate. The solvent was removed in vacuo to give the title compound.

Step B: Preparation of 2(S)-(*tert*-Butoxycarbonylamino)hexanal

A mechanically stirred suspension of lithium

aluminum hydride (5.00 g, 0.131 mol) in ether (250 mL) was cooled to -45°C under nitrogen. A solution of the product from Step A (28.3 g, 0.103 mol) in ether (125 mL) was added, maintaining the temperature below -35°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. A solution of potassium hydrogen sulfate (27.3 g, 0.200 mol) in water was slowly added, maintaining the temperature below -5°C. After quenching, the reaction was stirred at room temperature for 1h. The mixture was filtered through Celite, the ether evaporated, and the remainder partitioned between ethyl acetate and 2% potassium hydrogen sulfate. After washing with saturated brine, drying over magnesium sulfate and solvent removal, the title compound was obtained.

Step C: Preparation of *N*-(2,3-Dimethylphenyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine

2,3-Dimethylaniline (8.32 mL, 68.3 mmol) was dissolved in dichloroethane under nitrogen. Acetic acid was added to obtain pH 5, and sodium triacetoxyborohydride (17.2 g, 80.8 mmol) and crushed molecular sieves (4 g) were added. A solution of the product from Step B (13.3 g, 62.1 mmol) in dichloroethane (80 mL) was added slowly dropwise at 20°C. The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The aqueous layer was removed, the organic phase washed with saturated brine and dried over magnesium sulfate. Crystallization from hexane gave the title compound.

Step D: Preparation of (S)-5-*n*-butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-2,3-piperazinedione hydrochloride

The titled compound was prepared from the product of Step C using the procedures in Steps H, I, and J of Example 1. The product was purified by silica gel chromatography (30-50% acetone/CH2Cl2), then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the

titled product hydrochloride as a white powder.

FAB mass spectrum m/e 470 (M+1).
Analysis calculated for $C_{28}H_{31}N_5O_2 \cdot 1.0\ HCl \cdot 1.30\ H_2O$:
C, 63.52; H, 6.59; N, 13.23;
Found: C, 63.52; H, 6.60; N, 13.04.

EXAMPLE 3

1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,3-dione hydrochloride

Step A: Preparation of 3-(4-cyanobenzyl)pyridin-4-carboxylic acid methyl ester

A solution of 4-cyanobenzyl bromide (625 mg, 3.27 mmol) in dry THF (4mL) was added slowly over ~3 min. to a suspension of activated Zn (dust; 250 mg) in dry THF (2 mL) at O^o under an argon atmosphere. The ice-bath was removed and the slurry was stirred at room temperature for a further 30 min. Then 3-bromopyridin-4-carboxylic acid methyl ester (540 mg. 2.5 mmol) followed by dichlorobis(triphenylphosphine)nickel (II) (50 mg). The resultant reddish-brown mixture was stirred for 3h at ~40-45^{o}C. The mixture was cooled and distributed between EtOAc (100 ml) and 5% aqueous citric acid (50 mL). The organic layer was washed with H_2O (2X50 mL), dried with Na_2SO_4. After evaporation of the solvent the residue was purified on silica gel, eluting with 35% EtOAc in hexane to give 420 mg as a clear gum. FAB ms (M+l) 253.

Step B: Preparation of 3-(4-cyanobenzyl)-4-(hydroxymethyl)-pyridine

The title compound was obtained by sodium borohydride (300 mg) reduction of the ester from Step A (415 mg) in methanol (5 mL) at room temperature. After stirring for 4 h the solution was evaporated and the product was purified on silica gel, eluting with 2%

methanol in chloroform to give the title compound. FAB ms (M+1) 225.

Step C: Preparation of 3-(4-cyanobenzyl)-4-pyridinal

The title compound was obtained by activated manganese dioxide (1.0g) oxidation of the alcohol from Step B (240 mg, 1.07 mmol) in dioxane (10 mL) at reflux for 30 min. Filtration and evaporation of the solvent provided title compound, mp 80-83^{o}C.

Step D: Preparation of 1-(3-chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,3-dione hydrochloride

The titled compound is prepared from the pyridinal from Step C and the amine hydrochloride from Step I of Example 1 using the reductive alkylation procedured in Step J of Example 1. The product is purified by silica gel chromatography, then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride.

EXAMPLE 4

4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazine-2,3-dione hydrochloride

The titled compound was prepared using the same procedures described in Example 1, Step F through Step J, except that in Step F 2,3-dimethylaniline was used in place of 3-chloroaniline. The product of Step J was purified by silica gel chromatography (3-5% MeOH/CH_2Cl_2), then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo*. The titled product hydrochloride was isolated as a white powder.

FAB mass spectrum m/e 414 (M+1).

Analysis calculated for $C_{24}H_{23}N_5O_2 \cdot 1.0\ HCl \cdot 0.80\ H_2O$:

C, 62.08; H, 5.56; N, 15.08;
Found: C, 62.04; H, 5.63; N, 15.11.

EXAMPLE 5

(S) -5-Benzyl-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenyl-2,3-piperazinedione hydrochloride

Step A: Preparation of *N*-Methoxy-*N*-methyl 2(S)-(*tert*-butoxycarbonylamino)-3-phenylpropionamide

2(S)-(*tert*-Butoxycarbonylamino)-3-phenylpropionic acid (39.80 g, 0.150 mol), *N,O*-dimethylhydroxylamine hydrochloride (21.95 g, 0.225 mol), EDC hydrochloride (31.52 g, 0.165 mol) and HOBT (20.25 g, 0.150 mol) were stirred in dry, degassed DMF (200 mL) at 20°C under nitrogen. *N*-Methylmorpholine is added to obtain pH 7. The reaction was stirred overnight, the DMF distilled under high vacuum, and the residue partitioned between ethyl acetate and 2% potassium hydrogen sulfate. The organic phase was washed with saturated sodium bicarbonate, water, and saturated brine, and dried with magnesium sulfate. The solvent was removed in vacuo to give the title compound.

Step B: Preparation of 2(S)-(*tert*-Butoxycarbonylamino)-3-phenylpropionaldehyde

A mechanically stirred suspension of lithium aluminum hydride (6.59 g, 0.165 mol) in ether (1 L) was cooled to -45°C under nitrogen. A solution of the product from Step A (0.150 mol) in ether (150 mL) was added, maintaining the temperature below -35°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. A solution of potassium hydrogen sulfate (36.1 g, 0.265 mol) in water was slowly added, maintaining the temperature below -5°C. After quenching, the reaction was stirred at room temperature for 1h. The mixture was filtered through Celite, the ether evaporated, and the remainder partitioned

between ethyl acetate and 2% potassium hydrogen sulfate. After washing with saturated brine, drying over magnesium sulfate and solvent removal, the title compound was obtained.

Step C: Preparation of *N*-phenyl-2(S)-(*tert*-butoxycarbonylamino)-3-phenylpropanamine

Aniline (3.00 mL, 32.9 mmol) was dissolved in dichloroethane under nitrogen. The product from Step B was added (7.0 g, 29.91) and the reaction stirred for 1 h at room temperature. Sodium triacetoxyborohydride (9.51 g, 44.86 mmol) was added, and the pH adjusted to 5. The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The aqueous layer was removed, the organic phase washed with saturated brine and dried over magnesium sulfate. The title compound was obtained after chromatography on silica get with 8% ethyl acetate in hexane.

Step D: Preparation of (S) -5-Benzyl-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenyl-2,3-piperazinedione hydrochloride

The titled compound is prepared from the product of Step C using the procedures in Steps H, I, and J of Example 1. The product is purified by silica gel chromatography using 50% acetone in methylene chloride, followed by preparative HPLC using a 100 mm Waters PrepPak® reverse phase column (DeltaPak™ C_{18}, 50 mM, 100 Å), and pure product isolated by gradient elution using 0.1% trifluoroacetic acid in water 50% 0.1% trifluoracetic acid in acetonitrile. The combined pure fractions were evaporated, and the residue converted to the free base. This was dissolved in methylene chloride and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride. Anal. Calc. for $C_{29}H_{25}N_5O_2 \cdot 2\ H_2O \cdot Hcl$:

C, 63.56; H, 5.52; N, 12.78.

Found: C, 63.57; H, 5.07; N, 12.55.

EXAMPLE 6

(S)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione hydrochloride

Step A: Preparation of 1-(4-cyanobenzyl)-2-methyl-5-imidazolecarboxaldehyde

To a solution of 2-methylimidazole carboxaldehyde (20.48 g, 186 mmol) in 250 mL of DMF at 0 °C was added cesium carbonate (91 g, 279 mmol), then 4-cyanobenzyl bromide (36.5 g, 186 mmol). After 4 hours, the reaction was poured into 1.5 L of EtOAc, washed with water (3 x 1 L) and brine (0.5 L), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide a mixture of aldehyde regioisomers as a pale yellow solid. After filtration through a short column of silica gel (3% MeOH/CH2Cl2) and concentration *in vacuo*, the mixture was crystallized from hot 50% EtOAc/hexane to form the desired product as pale yellow needles (5.45 g).

Step B: Preparation of 2(S)-(*tert*-Butoxycarbonylamino)-4-methylpentanal

The titled compound was prepared from (S)-N-Boc-leucine using the procedures in Steps A and B of Example 2.

Step C: Preparation of 2(S)-(*tert*-butoxycarbonylamino)-*N*-[(3-trifluoromethoxy)phenyl]-4-methylpentanamine

The titled compound was prepared from the product of Step B using the procedure in Step C of Example 2, except that 3-(trifluoromethoxy)aniline was used in place of 2,3-dimethylaniline.

Step D: Preparation of (S)-4-[1-(4-cyanobenzyl)-2-methyl-

5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione hydrochloride

The titled compound was prepared from the product of Step C using the procedures in Steps H, I, and J of Example 1, except that in Step J the aldehyde from Step A of the present Example was used in place of 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde. The product was purified by silica gel chromatography (30-60% acetone/CH2Cl2), then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride as a white powder.

FAB mass spectrum m/e 539 (M+1).

Analysis calculated for $C_{28}H_{28}F_3N_5O_3 \cdot 1.0\ HCl \cdot 2.10\ H_2O$:
C, 54.79; H, 5.45; N, 11.41;
Found: C, 54.89; H, 5.66; N, 11.38.

EXAMPLE 7

4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-1-phenylpiperazine-2,3-dione hydrochloride

The titled compound was prepared from *N*-phenylethylenediamine using the procedures in Steps G, H, I, and J of Example 1, except that in Step J the aldehyde from Step A of Example 6 was used in place of 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde. The product was purified by silica gel chromatography (5-8% MeOH/CH2Cl2), then taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride as a white powder.

FAB mass spectrum m/e 400 (M+1).
Analysis calculated for $C_{23}H_{21}N_5O_2 \cdot 1.40$ HCl:
C, 61.35; H, 5.01; N, 15.55;
Found: C, 61.50; H, 5.02; N, 15.52.

EXAMPLE 8

1-(4-imidazolyl)-4-(2,3-dimethylphenyl)piperazine-2,3-dione hydrochloride

Step A: Preparation of 4-nitro-1-(triphenylmethyl)imidazole

To a solution of 4-nitroimidazole (7.28 g, 64.4 mmol) in 60 mL of dry DMF at 0°C was added triethylamine (9.87 mL, 70.8 mmol), then chlorotriphenylmethane (17.95 g, 64.4 mmol). After 5 minutes, the solution was warmed to room temperature. After 30 minutes, the reaction mixture was poured over ice, filtered, and washed with ice water. The resulting product was dried *in vacuo* next to P2O5 to provide the titled product as a white powder (22.29 g, 97% yield) which was sufficiently pure for use in the next step.

Step B: Preparation 4-amino-1-(triphenylmethyl)imidazole

Through a solution of the product from Step A (572 mg, 1.61 mmol) and 10% palladium on carbon (145 mg) was gently bubbled a balloon of hydrogen gas via syringe needle. After two hours, the reaction was flushed with nitrogen, then filtered through celite to remove the catalyst. The solution was concentrated *in vacuo* to provide the crude product as a fluffy white solid which was sufficiently pure for use in the next reaction.

Step C: Preparation of *N*-[2,2-diethoxy(ethyl)]-2,3-dimethylaniline

To a solution of 2,3-dimethylaniline (2.0 mL, 16.6 mmol) in 30 mL of dry DMF at room temperature was added cesium carbonate (5.4 g, 17 mmol), then bromoacetaldehyde diethylacetal

(2.50 mL, 16.6 mmol). The solution was warmed to 110°C, and stirred for four days. Sodium iodide (100 mg, 0.6 mmol) was added, and the reaction stirred for an additional 24 hours.. The reaction mixture was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product as a brown oil which was used directly in the next step without further purification.

<u>Step D</u>: Preparation of methyl *N*-[2,2-diethoxy(ethyl)]-*N*-(2,3-dimethylphenyl)oxalamide

A portion of the crude product from Step C (644 mg, 2.7 mmol) in 10 mL of EtOAc and 10 mL of saturated $NaHCO_3$ soln. was cooled to 0 °C. Methyl chlorooxalate (0.50 mL, 5.4 mmol) was added dropwise, and the reaction was maintained at 0 °C with stirring. After 15 minutes, the reaction was poured into EtOAc and washed with water, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide a brown oil. Purification by flash chromatography on silica gel (15-25% EtOAc/hexane) gave 592 mg of the desired product.

<u>Step E</u>: Preparation of methyl *N*-(2-oxoethyl)-*N*-(2,3-dimethylphenyl)oxalamide

To a solution of the ester from Step D (719 mg, 2.23 mmol) in 10 mL of dichloromethane at room temperature was added water (1 mL) and trifluoroacetic acid (1 mL). After 16 hours, the reaction was poured into EtOAc, washed with sat, $NaHCO_3$ soln. and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde (0.53 g, 100% yield) as a yellow oil which was sufficiently pure for use in the next step without further purification.

<u>Step F</u>: Preparation of 1-[1-triphenylmethyl-4-imidazolyl]-4-(2,3-dimethylphenyl)piperazine-2,3-dione

To a solution of the amine from Step B (200 mg,

0.615 mmol) in 2 mL of 1,2-dichloroethane at 0 °C was added 4Å powdered molecular sieves (400 mg), sodium triacetoxyborohydride (200 mg, 0.948 mmol) and aldehyde from Step E (144 mg, 0.613 mmol). The reaction was stirred overnight, allowing it to warm to room temperature. After 20 hours, the reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product (230 mg, 71% yield) was sufficiently pure for use in the next step without further purification.

Step G: Preparation 1-(4-imidazolyl)-4-(2,3-dimethylphenyl)-piperazine-2,3-dione hydrochloride

A solution of the product from Step F (260 mg, 0.50 mmol) and 4-cyanobenzylbromide (107 mg, 0.54 mmol) in 3 mL of EtOAc was refluxed overnight. The reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (3-5% MeOH/CH_2Cl_2) gave the desired product along with cyanobenzylated material. The product was taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride.

FAB mass spectrum m/e 285 (M+1).

Analysis calculated for $C_{15}H_{16}N_4O_2 \cdot 0.5\ HCl \cdot 0.70\ H_2O$:

C, 57.17; H, 5.72; N, 17.78;

Found: C, 57.26; H, 5.69; N, 15.94.

EXAMPLE 9

1-[1-(4-cyanobenzyl)-5-imidazolyl]-4-(2,3-dimethylphenyl)piperazine-2,3-dione hydrochloride

Step A: Preparation of 4-cyanobenzyl alcohol

To a solution of 4-cyanobenzaldehyde (1.97 g, 15.0 mmol) in 50 mL of ethanol at room temperature was added sodium borohydride (0.57 g, 15.0 mmol). After 4 days, the solution was quenched with saturated ammonoum chloride solution, then poured into EtOAc, washed with sat, $NaHCO_3$ soln. and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the product (1.82 g, 92% yield) as a white waxy solid which was sufficiently pure for use in the next step without further purification.

Step B: Preparation of 1-[1-(4-cyanobenzyl)-5-imidazolyl]-4-(2,3-dimethylphenyl)piperazine-2,3-dione hydrochloride

To a solution of 4-cyanobenzyl alcohol from Step A (153 mg, 0.291 mmol) in 1.0 mL of dichloromethane at -78 °C was added diisopropylethylamine (0.066 mL, 0.379 mmol), followed by triflic anhydride (0.053 mL, 0.316 mmol). After 20 minutes, a solution of diketopiperazine from Step F of Example 8 (153 mg, 0.291 mmol) in 1.0 mL dichloromethane was added dropwise via syringe. The reaction was allowed to warm to room temperature over 30 minutes, then concentrated in vacuo. The solution was taken up in 2 mL of methanol and heated to reflux for one hour, then cooled to room temperature, poured into EtOAc, washed with sat, $NaHCO_3$ soln. and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The product was purified by flash chromatography on silica gel (2-5% MeOH/CH_2Cl_2), taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride (30.8 mg) as a white powder.

FAB mass spectrum m/e 400 (M+1).

Analysis calculated for $C_{23}H_{21}N_5O_2 \cdot 1.90\ HCl \cdot 1.20\ H_2O$:

C, 56.34; H, 5.20; N, 14.28;

Found: C, 56.40; H, 5.18; N, 13.75.

EXAMPLE 10

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^3H]-farnesyl diphosphate ([^3H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^3H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in Examples 1, 2 and 4-8 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC_{50} of ≤10 μM.

EXAMPLE 11

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 12

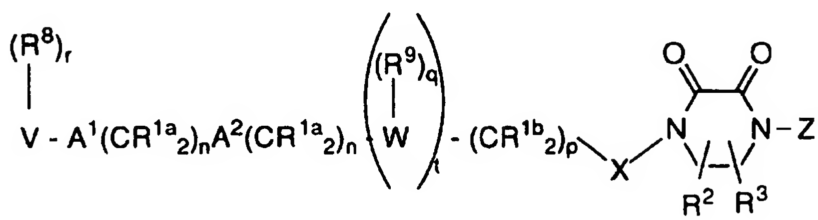
In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



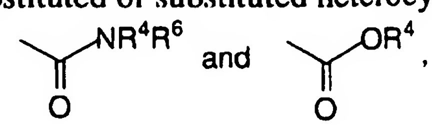
A

wherein:

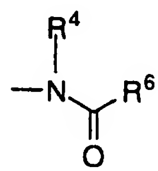
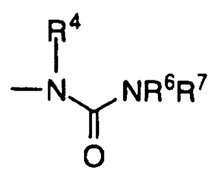
R^{1a} and R^{1b} are independently selected from:

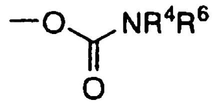
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

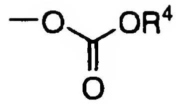
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

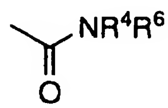


wherein the substituted group is substituted with one or more of:

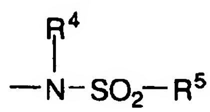
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^4$,
   c) $(CH_2)_pNR^4R^6$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl, or
   h) SR^5, $S(O)R^5$, SO_2R^5,
2) C_{3-6} cycloalkyl,
3) OR^4,
4) SR^5, $S(O)R^5$, or SO_2R^5,
5) $—NR^4R^6$,
6)  ,
7)  ,

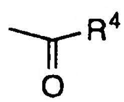
8)  ,

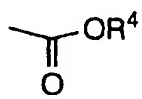
9)  ,

10)  ,

11) $-SO_2-NR^4R^6$,

12)  ,

13)  ,

14)  ,

15) N_3,

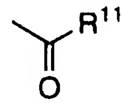
16) F, or

17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})- ;

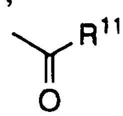
and R^2 and R^3 are optionally attached to the same carbon atom;

R^4, R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^4 and R^6 may be joined in a ring;
R^6 and R^7 may be joined in a ring;

R^5 is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is bond, $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

Z is selected from:

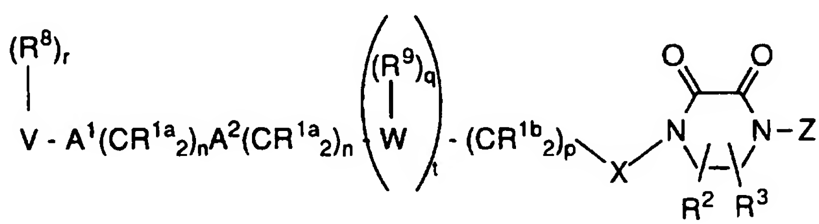
1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   b) aryl or heterocycle,
   c) halogen,
   d) OR^4,
   e) NR^4R^6,
   f) CN,
   g) NO_2,
   h) CF_3;
   i) $-S(O)_mR^5$,
   j) $-C(O)NR^4R^6$, or
   k) C_3-C_6 cycloalkyl; and
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
   a) C_{1-4} alkoxy,
   b) NR^4R^6,
   c) C_{3-6} cycloalkyl,

d) $-NR^4C(O)R^6$,
e) HO,
f) $-S(O)_mR^5$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
t is 0 or 1; and
u is 4 or 5;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 of the formula A:



A

wherein:

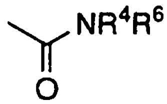
R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from

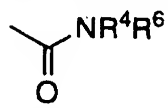
unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and $-N(R^{10})_2$;

R^3 is selected from H and CH_3;

R^2 is selected from H;


;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^4,
4) SR^5, SO_2R^5, or
5) 
;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$- and $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl and isoquinolinyl;

X is $-CH_2-$ or $-C(=O)-$;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   b) aryl or heterocycle,
   c) halogen,
   d) OR^4,
   e) NR^4R^6,
   f) CN,
   g) NO_2,
   h) CF_3;
   i) $-S(O)_mR^5$,
   j) $-C(O)NR^4R^6$, or
   k) C_3-C_6 cycloalkyl; and
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted

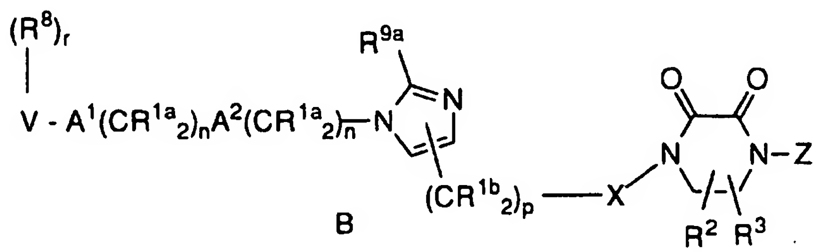
C3-C6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^4R^6,
c) C_{3-6} cycloalkyl,
d) $-NR^4C(O)R^6$,
e) HO,
f) $-S(O)_mR^5$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
t is 0 or 1; and
u is 4 or 5;

or an optical isomer or pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula B:



wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

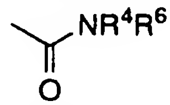
a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

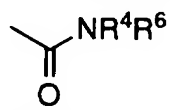
R^3 is selected from H and CH_3;

R^2 is selected from H;



;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^4,
4) SR^5, SO_2R^5, or
5) 

;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^{10}$-, O, $-N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is $-CH_2$- or -C(=O)-;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
   - a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
   - b) aryl or heterocycle,
   - c) halogen,
   - d) OR^4,
   - e) NR^4R^6,
   - f) CN,
   - g) NO_2,
   - h) CF_3;
   - i) $-S(O)_mR^5$,
   - j) $-C(O)NR^4R^6$, or
   - k) C_3-C_6 cycloalkyl; and

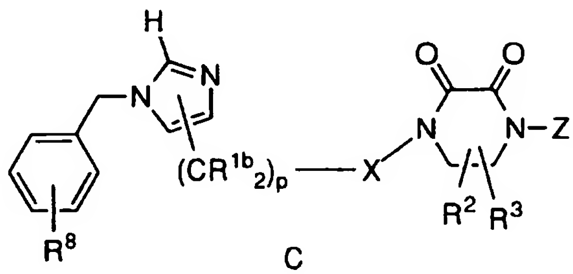
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
   - a) C_{1-4} alkoxy,
   - b) NR^4R^6,
   - c) C_{3-6} cycloalkyl,
   - d) $-NR^4C(O)R^6$,
   - e) HO,
   - f) $-S(O)_mR^5$,
   - g) halogen, or
   - h) perfluoroalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 3 of the formula C:



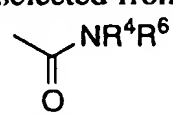
C

wherein:

R^{1b} is independently selected from:

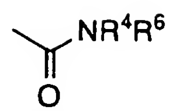
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from H and CH_3;
R^2 is selected from H;


;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^4,
4) SR^5, SO_2R^5, or

5) 

;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 and R^6 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is -CH_2- or -$C(=O)$-;

Z is selected from:

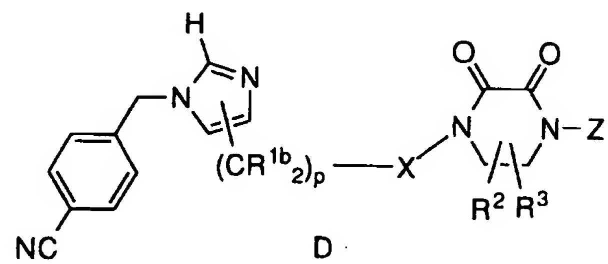
1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
    a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^4R^6, C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^5$, or $-C(O)NR^4R^6$,
    b) aryl or heterocycle,
    c) halogen,
    d) OR^4,
    e) NR^4R^6,
    f) CN,
    g) NO_2,
    h) CF_3;
    i) $-S(O)_mR^5$,
    j) $-C(O)NR^4R^6$, or
    k) C_3-C_6 cycloalkyl; and
2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
    a) C_{1-4} alkoxy,
    b) NR^4R^6,
    c) C_{3-6} cycloalkyl,
    d) $-NR^4C(O)R^6$,
    e) HO,
    f) $-S(O)_mR^5$,
    g) halogen, or
    h) perfluoroalkyl;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 4 of the formula D:



D

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^2 and R^3 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^4 and R^6 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^5 is selected from:
C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:
a) C_{1-4} alkoxy,

b) halogen, or
c) aryl or heterocycle;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is $-CH_2-$ or $-C(=O)-$;

Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic heteroarylmethyl, mono- or bicyclic arylsulfonyl or mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^4R^6,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^5$, or
   g) $-C(O)NR^4R^6$,
2) aryl or heterocycle,
3) halogen,
4) OR^4,
5) NR^4R^6,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^5$,
10) $-C(O)NR^4R^6$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or pharmaceutically acceptable salt thereof.

6. A compound which inhibits farnesyl-protein transferase which is:

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,3-dione

(S)-5-*n*-butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-2,3-piperazinedione

1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,3-dione

4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazine-2,3-dione

(S) -5-Benzyl-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenyl-2,3-piperazinedione

(S)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione

4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-1-phenylpiperazine-2,3-dione

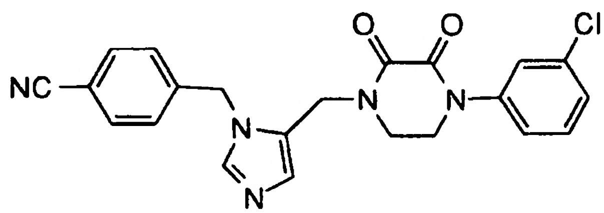
1-(4-imidazolyl)-4-(2,3-dimethylphenyl)piperazine-2,3-dione

1-[1-(4-cyanobenzyl)-5-imidazolyl]-4-(2,3-dimethylphenyl)piperazine-2,3-dione

or a pharmaceutically acceptable salt or optical isomer thereof.

7. The compound according to Claim 6 which is:

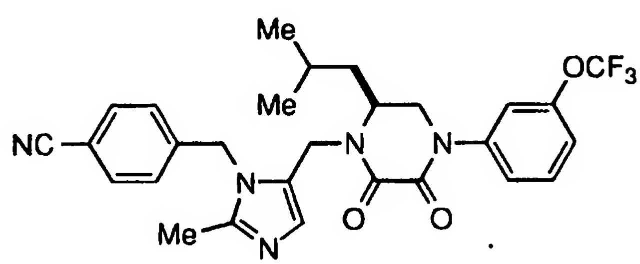
4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,3-dione



or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6 which is:

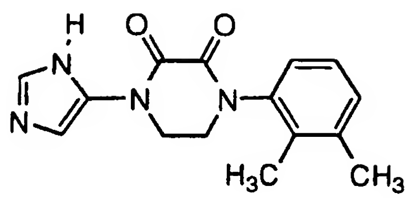
(S)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-5-(2-methyl-1-propyl)-1-[3-(trifluoromethoxy)phenyl]-2,3-piperazinedione



or a pharmaceutically acceptable salt or optical isomer thereof.

9. The compound according to Claim 6 which is:

1-(4-imidazolyl)-4-(2,3-dimethylphenyl)piperazine-2,3-dione



,

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

11. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

12. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

13. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

15. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

22. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

23. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

24. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

25. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

26. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

27. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

28. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05058

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 403/00; A61K 31/495
US CL :544/359; 514/255
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/359; 514/255

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,287,195 A (HEERES ET AL) 01 September 1981, see entire document.	1-13
A	US 4,456,685 A (HEERES ET AL) 26 June 1984, see entire document.	1-13
A	US 5,478,934 A (YUAN ET AL) 26 December 1995, see entire document.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 JULY 1997

Date of mailing of the international search report

06 AUG 1997

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